VERIFICATION OF A TRANSLATION

I, the below-named translator, hereby declare that:

My name and post office address are as stated below:

I am knowledgeable in the French and English languages, and that I believe the attached English translation of the French-language text of French patent application 99/00330 of January 14, 1999 is a true and complete translation of said text.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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November 2002, 20th
Date

NOVEL STABILIZED ACTIVATED CARBAMATES, THEIR PROCESS OF PREPARATION AND THEIR USE FOR THE PREPARATION OF UREAS

The invention has for its object novel stable activated carbamates, their process of preparation and their use for the preparation of urea.

The synthesis and applications of substituted ureas has for several years undergone great development. These compounds are present in a certain number of active principles now under development in the pharmaceutical industry as protease inhibitors of VIH, antagonists of the CCK-B receptor, or antagonists of endothelin [1]. Moreover, the oligoureas have been introduced as "scaffolds" for the creation of ß-sheets [2] or as mimics of the peptide skeleton [3]. The methods of formation of substituted ureas rely on the reaction of amines with carbonylation agents [4], with isocyanates [5] or with carbamates [6].

In the field of research looking toward the development of new compounds with immunomodulatory activity, there is needed a simple method, not requiring the use of phosgene or of one of its derivatives, to produce easily peptidic analogs containing ureas or urea oligomers. In 1995, the Burgess group described for the first time the synthesis in solid phase of oligoureas. This was based on the use of isocyanate synthons derived from N-protected mono-phthalimide diamines. This strategy requires the preparation of protected mono-phthalimide diamines precursors and uses triphosgene as the carbonylation agent to obtain the corresponding isocyanate [3a,3b]. In a similar approach, the Schultz group used azido 4-nitrophenyl carbamates as pre-activated synthons [3c,3d]. More recently, 4-nitrophenyl carbamates obtained by the reaction of Boc-protected N-substituted ethylenediamines with 4-nitrophenyl chloroformate have been described as synthons for the synthesis of urea-peptoids by the Liskamp group [3e]. In short, there does not exist at present an easy synthesis route for activated monomers obtained from amino acids protected or not by a Fmoc, Boc or Z group, avoiding the use of phosgene (or its derivatives) and permitting the synthesis of urea oligomers as well as the easy incorporation of urea patterns in peptides. The activated carbamates are generally prepared by the reaction of amines with carbonates [4c] or chloroformates [3e,6b], or by reaction of isocyanates with alcohols [6a].

One of the aspects of the invention is to provide novel stable activated carbamates.

One of the other aspects of the invention is to provide novel isocyanates.

One of the other aspects of the invention is to provide a novel process for the preparation of urea, cyclic or not.

One of the other aspects of the invention is to provide novel ureas, cyclic or not.

Generally speaking, the invention has for its object the use of isocyanates obtained from amino acid derivatives for the preparation and if desired the isolation of stable activated carbamates.

By "amino acid derivatives" is meant amino acids (alpha-, beta-, gamma-, delta-aminated, or the like) whose primary or secondary amine function can be protected by a group selected to give a tertiary amine function, urethane, amide, urea, nitro or phthalimide.

By "activated carbamate" is meant a carbamate capable of reacting with primary or secondary amines or with alcohols in the presence or not of a base in an organic solvent and generally at ambient temperature.

By "stable carbamate" is meant a stable carbamate because it is isolable, purifiable and can be stored (preferably at 4°C) for a period of at least 3 months without noticeable degradation. The stability can be measured for example by the following test: HPLC or thin layer chromatography.

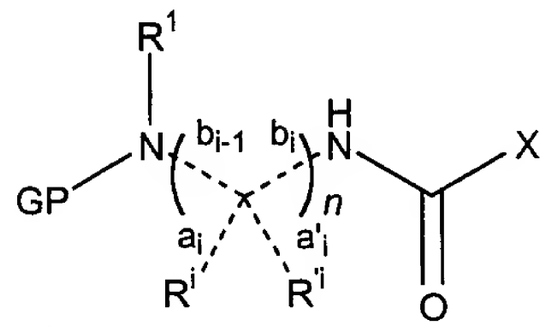
By "isolation" is meant the process of separation of the desired product from all of the impurities present in the reaction mixture (the latter can be for example: an excess of one of the reagents used to carry out the reaction, symmetrical urea, the amine obtained by the rearrangement of isocyanate in the presence of water) and the recovery of the thus-purified product in a form permitting it to be stored (preferably at 4°C) for a long period (several months, at least 3 months) without noticeable decomposition.

According to a preferred embodiment, the invention relates to the use of isocyanates or of stable activated carbamates defined above, for the preparation of substituted ureas, cyclic or not, particularly of oligomers of ureas, cyclic or not, or for the preparation of peptides or pseudo-peptides containing urea designs, cyclic or not.

The expression "urea oligomers" means a successive chain of motifs interconnected by urea linkages (at least two)

For example: NH_2-CHR_1-CHR'_1-NH-CO-NH-CHR_2-CHR'_2-NH-CO-NH-CHR_3-CHR'_3-$CONH_2$.

According to another preferred embodiment of the invention, the compounds have the formula (I):



(I)

in which

– "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

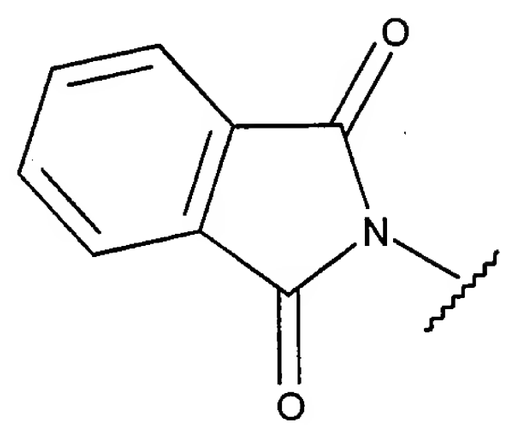
* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form parts of aromatic rings,

– GP is a protective group selected from:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
* aryl, particularly phenyl,
* urea (GP = RNHCO), preferably R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide ($R^1 = Ø$)



* O_2 (corresponds to a nitro group as masked form of the amine), $R^1 = Ø$

– the groups R_1, R_i, R'_i and R can each represent independently one of the other:

hydrogen,

halogen,

the side chain of amino acid selected from natural or synthetic amino acids,

an alkyl (C1-C20) group, substituted or not with one or several of the following substituents:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an alcoxy group OR_a

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the group X represents a group conferring on the compound of formula I an activated carbamate structure, selected particularly from phenols, if desired substituted with at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compound of formula (I) having the following property:

– if one or several asymmetric carbons are present in the formula (I), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R''^i can also be defined on the basis of intramolecular cyclizations which are as follows:

1/ cyclization between R^i and R''^i

2/ cyclization between R^i or R''^i and R^{i+kc} (where kc is a positive whole number, preferably from 1 to 3)

3/ cyclization between R^1 and R^i or R''^i wherein preferably i = 1, 2, 3 or 4,

provided that the compound of formula (I) is different from the following compounds, in which:

- n=2, GP=Boc, R_1 = isobutyl, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol,
- n=2, GP=Boc, R_1 = benzyl, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol,
- n=2, GP=Boc, R_1 = CH_2-p-C_6H_4O*t*-Bu, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol,
- n=2, GP=Boc, R_1 = H, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol.

The first bond b_1 and the last b_{n+1} each connected to a nitrogen atom, are always single bonds: * b_1 and b_{n+1} are always single bonds (s).

If a b_i bond is double, this implies that the adjacent bonds b_{i-1}, b_{i+1}, a_i and a_{i+1} are single bonds and that the bonds a'_i and a'_{i+1} do not exist:

* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s

If a b_i bond is triple, this implies that the adjacent bonds b_{i-1}, b_{i+1} are single bonds and that the bonds a_i, a'_i, a_{i+1} and a'_{i+1} do not exist:

* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s

If an a_i bond is double, this means that the adjacent bonds b_{i-1} and b_i are single bonds and that the bond a'_i does not exist.

* if a_i = d, then b_{i-1} and b_i = s.

The symbol Ø corresponds to the absence of the bond to which it relates.

The expression "certain of the bonds could also be part of aromatic rings, substituted or not" can be explained in the following manner. Three cases can occur:

$n \geq 2$: the bonds a_i, a_{i+1}, and b_i belong to the aromatic cycle; the bond b_{i+1} is in the ortho position relative to the b_{i-1} bond.

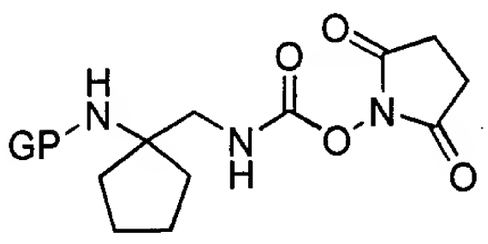
$n \geq 3$: the bonds a_i, a_{i+2}, b_i and b_{i+1} belong to the aromatic cycle; the b_{i+2} bond is in the meta position relative to the b_{i-1} bond.

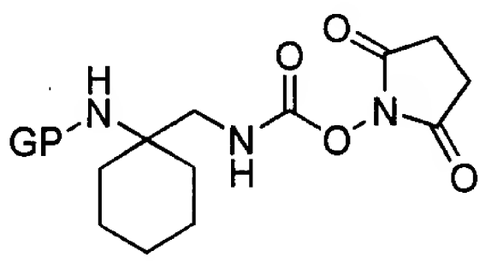
$n \geq 4$: the bonds a_i, a_{i+3}, b_i, b_{i+1} and b_{i+2} belong to the aromatic cycle; the bond b_{i+3} is in the ortho position relative to the b_{i-1} bond.

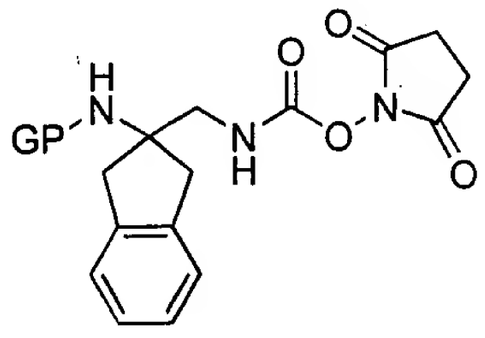
If there are cyclizations between R^I, R^i and R^{ii}, they can be illustrated in the following manner:

1/ Cyclization between R^i and R^{ii}:

by way of illustration, the three following molecules, in which n=2, contain a cyclization between R^2 and R^{i2}

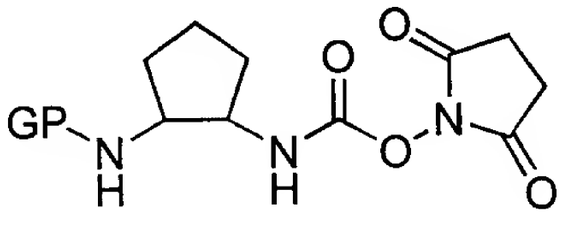
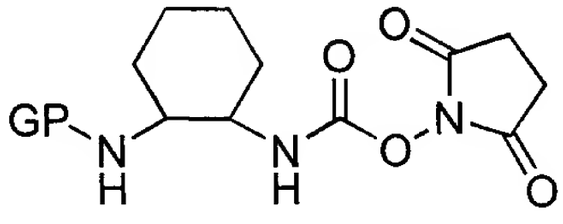






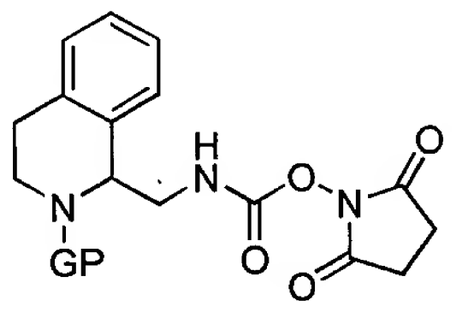
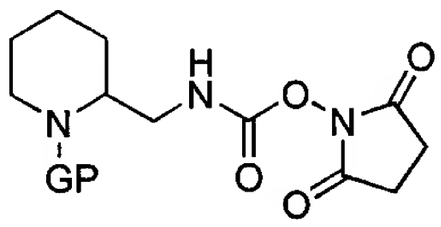
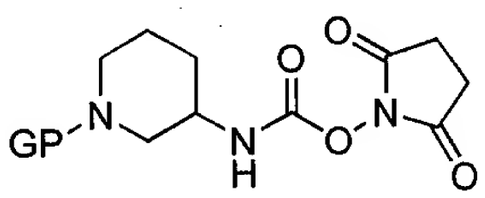
2/ Cyclization between R^i (or R'^i) and R^{i+k} (where k can be a whole positive number comprised between 1 and 3):

by way of illustration, the three following molecules in which n=2, contain a cyclization between R^2 and R^3 (in this case k is equal to 1)

3/ Cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4:

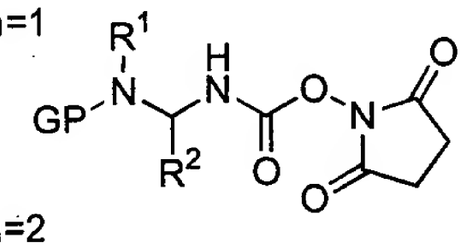
by way of illustration, the three following molecules in which n=2, contain a cyclization between R^1 and R^2 (or R^1 and R^3)

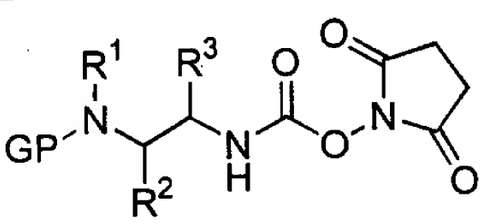
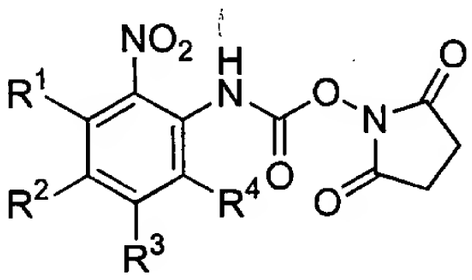
The compounds of formulas (I) are activated carbamates derived from N-protected amino acids of formula (IX) defined hereafter and which can be obtained from isocyanates of formula (II) defined hereafter.

A group of preferred compounds of formula (I) are those in which $1 \geq n \geq 4$, X = N-hydroxysuccinimide and GP is an urethane or acyl group such as defined above, and particularly the following compounds, in which GP is advantageously Boc, Fmoc or O_2,

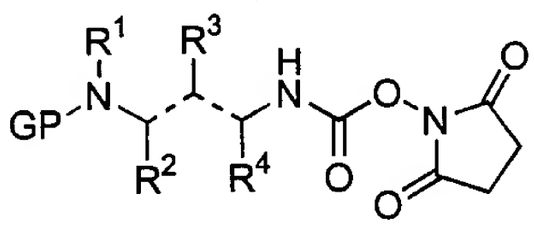
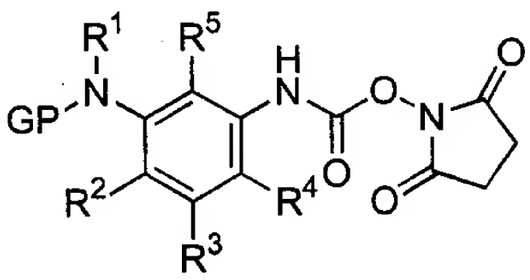
n=1



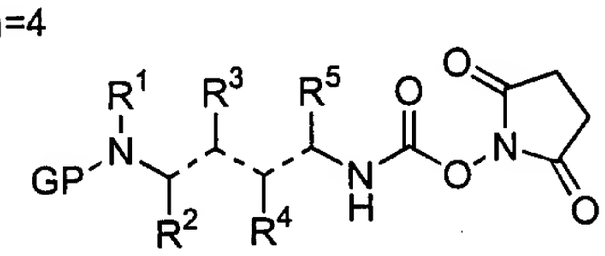
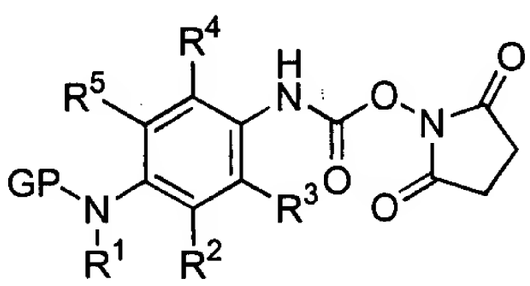
n=2

n=3

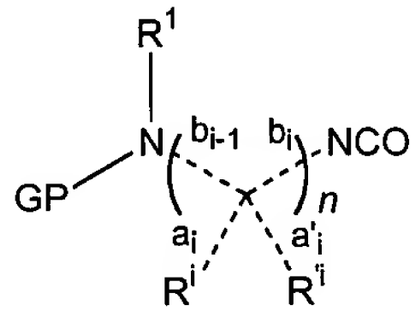



n=4

the binding with a broken line, representing a simple or double binding, with the proviso that a double binding is not contiguous to another double binding.

The invention also relates to isocyanates having the above formula (II)



(II)

in which

– "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "i" is a number varying from 2 to n+1,

– a_i and a'_i, represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s)
* if b_i = d then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d then b_{i-1} and b_i = s

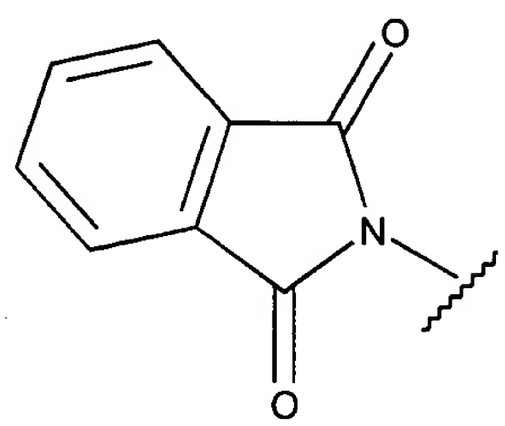
certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– GP is a protective group chosen among:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$)
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
*aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

*phtalimide (R1 = Ø)



* O_2 (corresponds to a nitro group as a masked form of the amine), R^1 = Ø

– the groups R_1, R_i, R'_i and R can each represent independently one of the other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents chosen among:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/-NHR_a

7/-NH_2

8/-$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a alcoxy group

a NH_2 group

an OH group,

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

the compound of formula (I) having the following property:

– if one or several asymmetric carbons are present in the formula (I), then their configuration can be independently either R (rectus) or S (sinister),

- the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a whole positive number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

– provided that the compound of formula (II) is different from the compounds in which:

– n = 1, GP = Boc or benzyloxycarbonyl, $R_1 = Ø$

– n = 2, GP = phtalimide, $R_1 = Ø$, R_3 = benzyl, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, R_3 = methyl, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = H$, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2$*i*-Pr, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2COO$*t*-Bu, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1=Ø$, $R_3=CH_2\ CH_2\ CH_2\ CH_2NHBoc$, $R'_2=R_2=R'_3=H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2\ CH_2\ CH_2NHCNH$(N-Mtr), $R'_2 = R_2 = R'_3 = H$, (Mtr = 4-methoxy-2,3,6-trimethyl-benzenesulphonyl)

– n = 2, GP = Boc, R_1 = benzyl, $R_2 = R'_2 = R_3 = R'_3 = H$

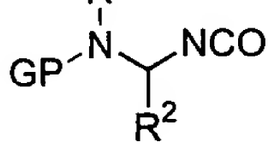
– n = 2, GP = Boc, R_1 = *i*-Bu, $R_2 = R'_2 = R_3 = R'_3 = H$

– n = 2, GP = Boc, $R_1 = H$, $R_2 = R'_2 = R_3 = R'_3 = H$

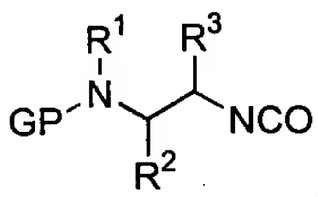
The isocyanates of formula (II) are the precursors used in the synthesis of compounds of formula (I) and can be obtained from N-protected amino acid derivatives of formula (IX) defined hereafter.

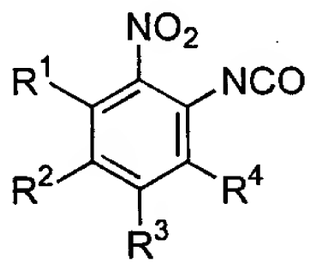
A group of advantageous compounds of formula (II) are those in which $1 \leq n \leq 4$ and GP is an urethane or acyl group as defined according to claim 5, and particularly the following compounds, particularly those for which GP= Boc and Fmoc,

n=1

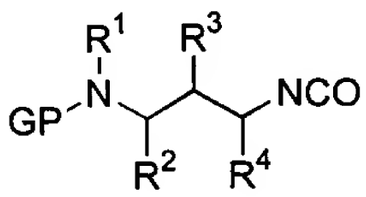


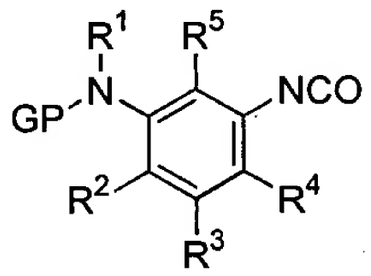
n=2



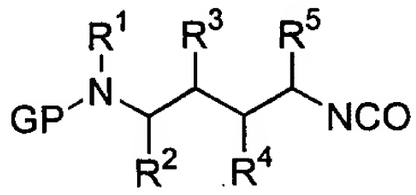


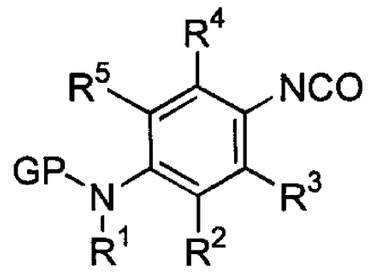
n=3





n=4





In compounds of formula (I) and (II) of the invention, the aryl group is advantageously chosen among:

1/ phenyl

2/ naphtyl

3/ indenyl

4/ thiophenyl

5/ benzothiophenyl

6/ furanyl

7/ benzofuranyl

8/ pyridyl

9/ indolyl

10/ pyrollyl

or the aryl group non-substituted or substituted with 1 to 6 substituents chosen particularly among:

1/ alkyl of 1 to 10 carbon atoms

2/ halogen

3/ alcoxy of 1 to 10 carbon atoms

4/ hydroxyl

5/ amine of 1 to 10 carbon atoms

6/ ester of 1 to 10 carbon atoms

7/ nitrile

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ nitro

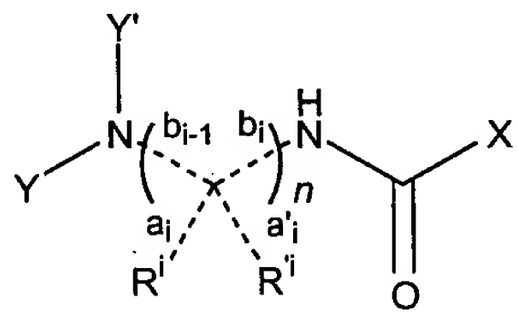
10/ urea of 1 to 10 carbon atoms

11/ amide of 1 to 10 carbon atoms

12/ guanidine

13/ carboxylic acid of 1 to 10 carbon atoms.

The invention also relates to compounds of the formula (III)



(III)

in which

– "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– a_i and a'_i, represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s),

* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s

* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s,
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– the groups R_1, R_i and R'_i can each represent independently one of the other:

hydrogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the groups Y and Y' can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide bonds)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\Psi_1[*]\text{-}\ldots\text{-}\Psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\Psi_k[*]\text{-}\ldots\Psi_{p-1}[*]C(Z'_p)(Z''_p)\text{-}\Psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

– "k" is a whole number varying from 1 to p,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH{=}CH_2$),

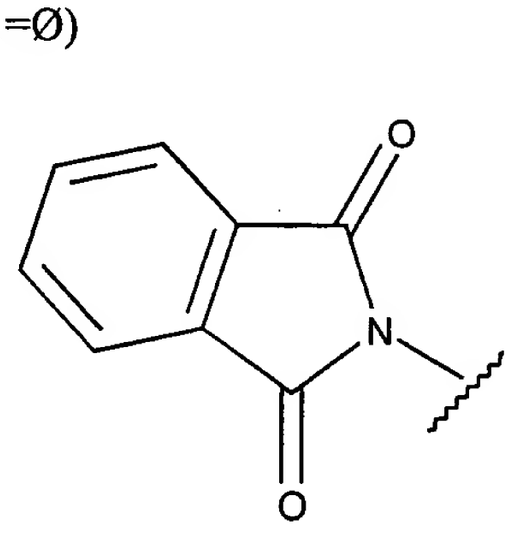
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R1=Ø)



* biotin

– Z_k, Z'_k and Z''_k can each represent independently one of the other: hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids

a (C1-C20) alkyl group unsubstituted or substituted by one or several constituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

– -ψ_k[*]- are independently either peptidic linkages CO-NH or bonds of different chemical nature selected particularly from the following list, which is not limiting:

ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO- ; -NHCONH- ; -$COCH_2$ - ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F_k')$CONH-

F_k and F_k' representing, independently from each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

2/ an amino acid residue or an amino acid chain:

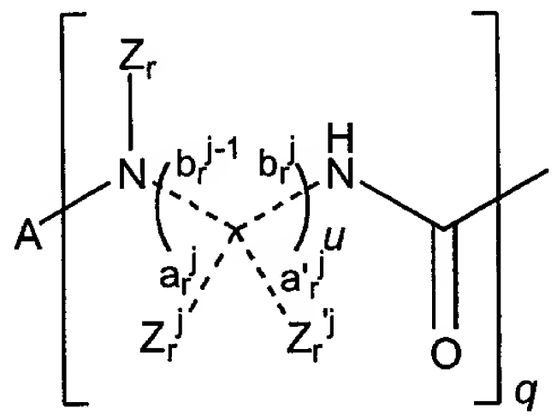
$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}CO\text{-}N(Z_2)\text{-}\ldots\text{-}CO\text{-}N(Z_k)\text{-}C(Z'_k)(Z''_k)\text{-}CO\text{-}N(Z_{k+1})\text{-}\ldots CO\text{-}N(Z_m)\text{-}C(Z'_m)(Z''_m)\text{-}CO\text{-}$

– "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– k is a whole number varying from 1 to m,

– A defined as above

3/ an oligomer of urea having the following formula:



– "u" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably 1 to 50, and particularly 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined in the following manner: j always takes the whole values comprised from 2 to u+1,

– or "r" is a whole parameter greater than or equal to 1, always taking values comprised from 1 to q,

– "a_r^j and a'^j_r", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s)
* if $b_r^j = d$, then a_r^j and $a_r^{j+1} = s$; a'^j_r and $a'^{j+1}_r = \emptyset$; b_r^{j-1} and $b_r^{j+1} = s$

* if $b_r^j = t$, then a_r^j and $a_r^{j+1} = \emptyset$; $a'_r{}^j$ and $a'_r{}^{j+1} = \emptyset$; b_r^{j-1} and $b_r^{j+1} = s$
* if $a_r^j = d$, then b_r^{j-1} and $b_r^j = s$

certain of these bonds can also form a part of aromatic rings,

– A defined as above

– Z_r, Z_r^j, Z'^j_r are defined independently as above for R^1, R^i, R'^i,

– the X group represents a group giving to the compound of formula I an activated carbamate structure, selected particularly from phenols, if desired substituted by at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

– N-hydroxysuccinimide
– phenol
– pentafluorophenol
– pentachlorophenol
– p-nitrophenol
– 2,4-dinitrophenol
– 2,4,5-trichlorophenol
– 2,4-dichloro-6-nitrophenol
– hydroxy-1,2,3-benzotriazole
– 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
– 7-aza-1-hydroxybenzotriazole (HOAt)
– 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compound of formula (III) having the following property:

– if one or several asymmetric carbons are present in the formula (III), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4.

As an example of a pseudopeptide entering into the definition of Y, can be cited:

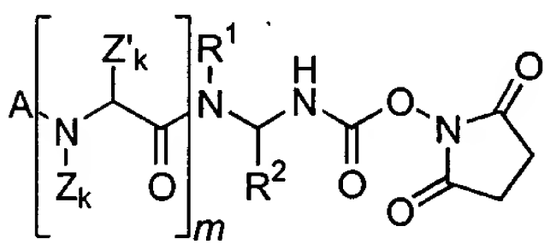
Boc-Ala-Ala-Gly-Ile-Gly-[CH_2NH]-Ile-

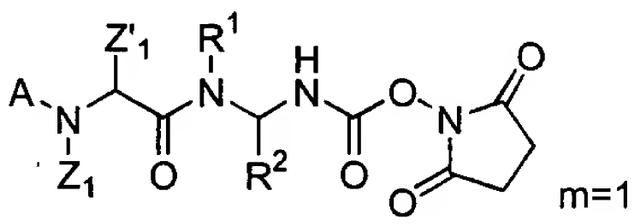
(pseudo-hexapeptide containing a bond of the reduced type between Gly and Ile)

The compounds of formula (III) are activated carbamates analogous to the compounds of formula (I) in which the protective group is replaced for example by an amino acid chain, a pseudopeptide, or an oligomer of urea. They can be obtained from corresponding isocyanates of formula (IV).

An advantageous group of compounds of formula (III) is constituted by those in which $1 \leq 4 \leq$, X = N-hydroxysuccinimide and GP is an urethane or acyl group and particularly the following compounds in which q and m are comprised from 1 to 10, and preferably equal to 1 or 2, and more particularly those in which GP = Boc and Fmoc or O_2,

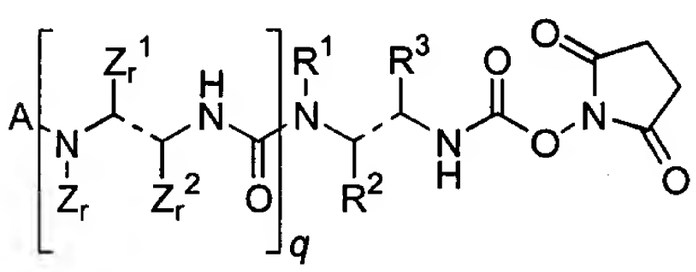
n=1

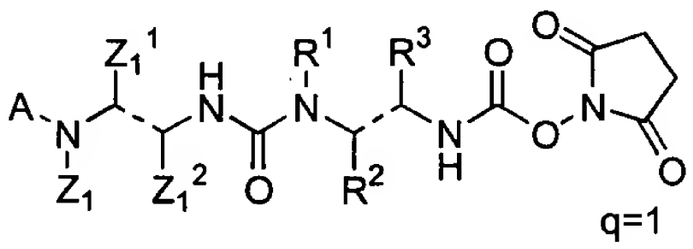




m=1

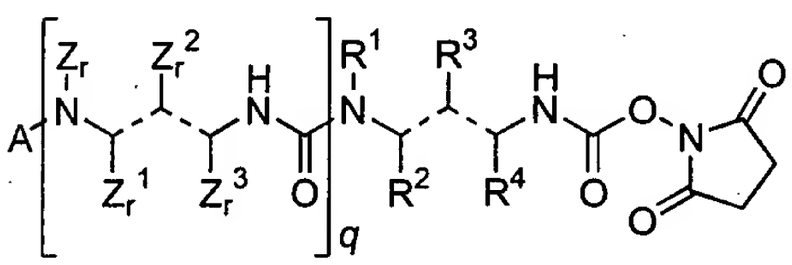
n=2

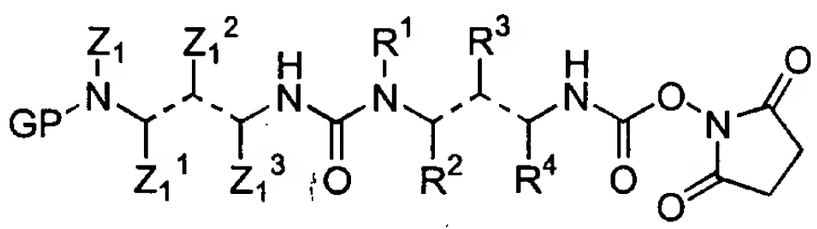




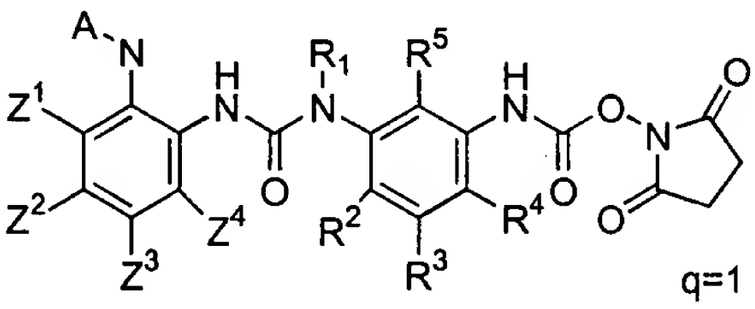
q=1

n=3



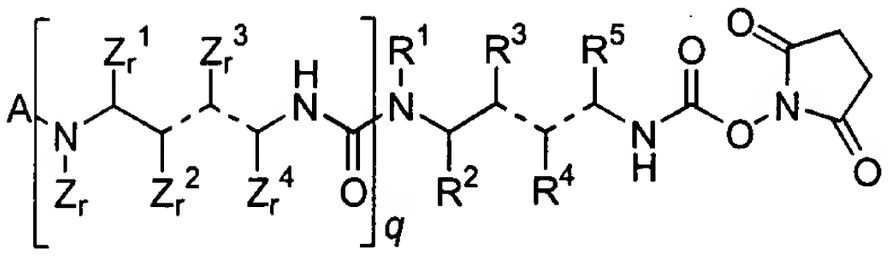


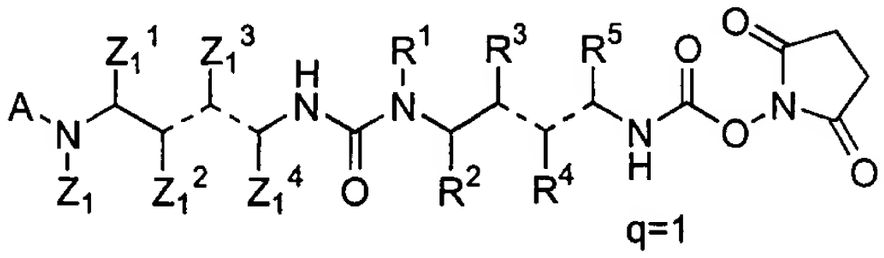
q=1



q=1

n=4

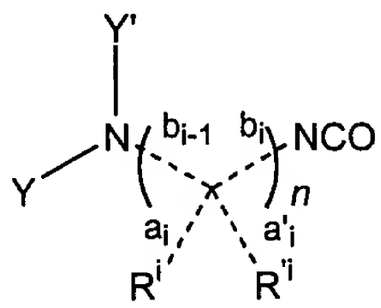




q=1

the broken lines corresponding to single or double bonds, provided that two double bonds are not contiguous.

The invention also relates to compounds of formula (IV)



(IV)

in which

– "n" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– a_i and a'_i represented by a broken line are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}" represented by a broken line are covalent bonds which can be single (s), double (d) or triple (t) with the proviso that:

* b_1 and b_{n+1} are always single bonds (s)
* if b_i = d then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen

halogen

the side chain of an amino acid selected from natural or synthetic amino acids

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents selected from:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

A-$N(Z_1)$-$C(Z'_1)(Z''_1)$-$\Psi_1[*]$-…- $\Psi_{k-1}[*]$-$C(Z'_k)(Z''_k)$-$\Psi_k[*]$-…$\Psi_{p-1}[*]C(Z'_p)(Z''_p)$- $\Psi_p[*]$-

– "p" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "k" is a whole number varying from 1 to p,

– or A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),

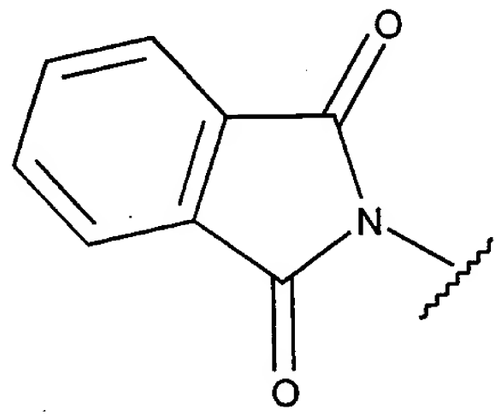
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R1=Ø)



* biotin

– Z_k, Z'_k and Z''_k can each represent and independently:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, substituted or unsubstituted with one or several substituents from the following:

1/ $-COOR_b$

2/ $-CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ $-NHR_b$

6/ $-NH_2$

7/ $-NH(CO)R_b$

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 halogen atoms

$-OR_b$

$-COOR_b$

$-CONHR_b$

$-CONH_2$

$-CH_2COOR_b$

$-CH_2CONHR_b$

$-CH_2CONH_2$

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– $-\Psi_k[*]-$ are independently either peptide linkages CO-NH, or linkages of different chemical nature selected particularly from the following list:

$\psi_k[*]- = -CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; $-NHCO-$; $-NHCONH-$; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF_k'-$; $-CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently from each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

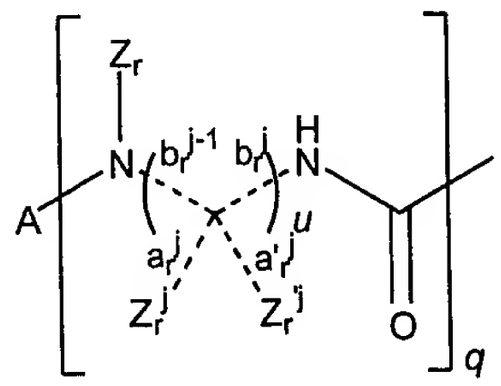
$A-N(Z_1)-C(Z'_1)(Z''_1)-CO-N(Z_2)-\ldots-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-\ldots CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-$

– "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above,

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably 1 to 50, and preferably 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably 1 to 50, and preferably 1 to 10,

– "j" is a whole parameter greater than or equal to 2, defined as follows: "j" takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s)
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are independently defined as previously for R^1, R^i, R'^i,

the compound of formula (IV) having the following property:

– if one or several asymmetric carbons are present in the formula (IV), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R'^i

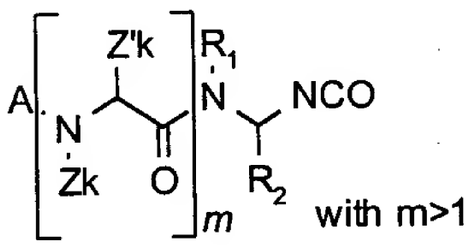
2/ cyclization between R^i (or R'^i) and R^{i+kc} (where kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4.

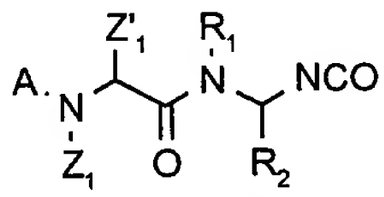
The isocyanates of formula (IV) can be used as precursors for the synthesis of the compounds of formula (III) and can be obtained from compounds of the formula (X).

An advantageous group of compounds of formula (IV) are those in which $1 \leq n \leq 4$ and A is an urethane or acyl group as defined according to claim 8, and particularly the following compounds for which q and m are comprised from 1 to 10 and preferably equal to 1 or 2, and particularly those for which A = Boc and Fmoc, and O_2,

n=1

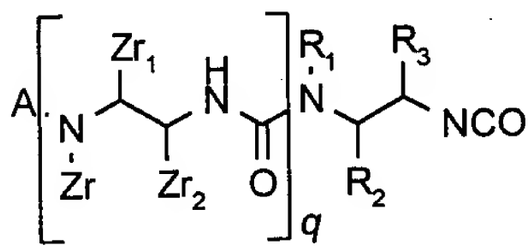


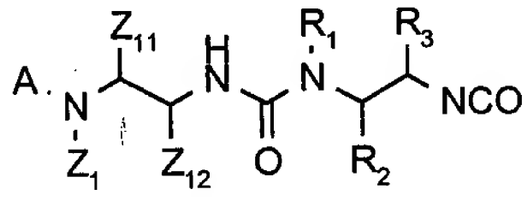
with m>1



m=1 with A different from Boc (tertbutoxycarbonyl) and from benzyloxycarbonyl

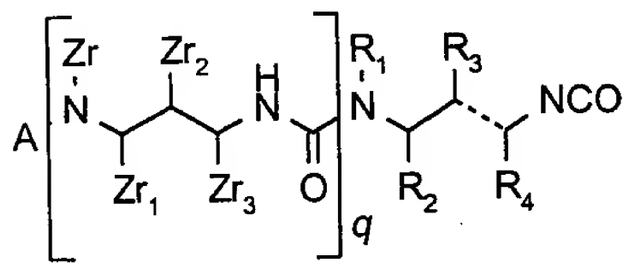
n=2

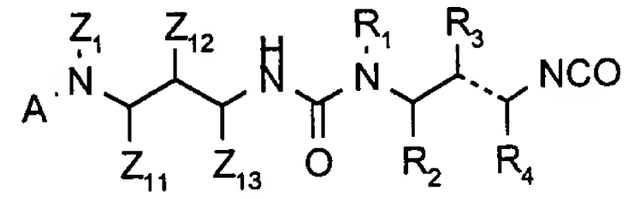




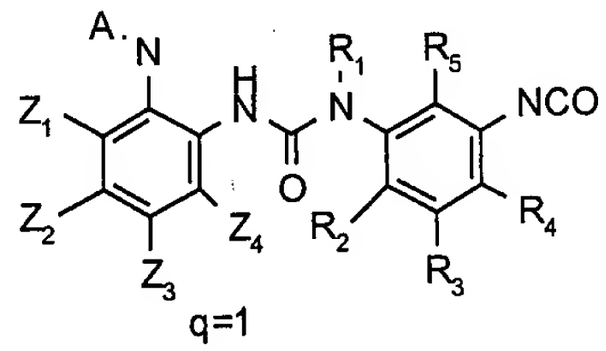
q=1

n=3



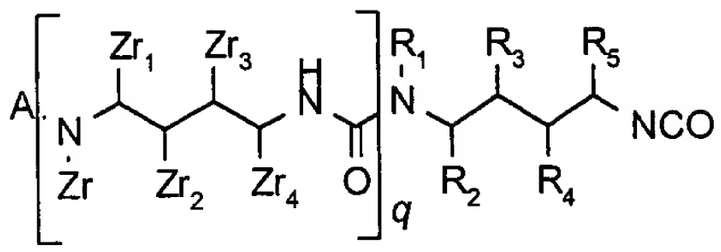


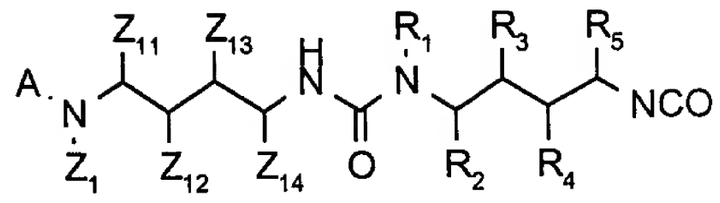
q=1



q=1

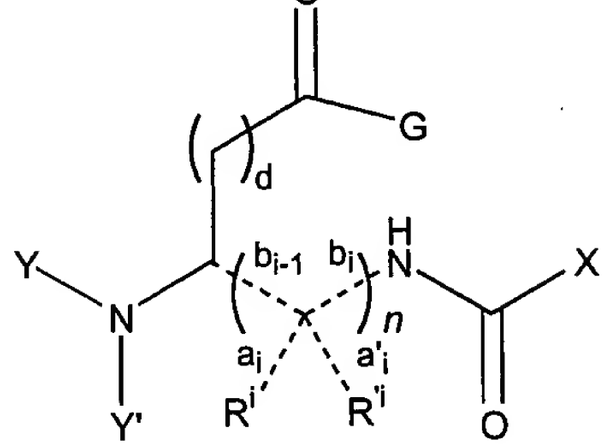
n=4





q=1

The invention also relates to compounds of the formula (V)



(V)

in which

– "n" is a whole number greater than or equal to 1, particularly from 1 to 4 and preferably from 1 to 2,

– "d" is a whole number comprised between 0 and 4, preferably equal to 0 or 1,

– "i" is a number varying from 2 to n+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds can also form a part of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\psi_1[*]\text{-}\ldots\text{-}\psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\psi_k[*]\text{-}\ldots\psi_{p-1}[*]\text{-}C(Z'_p)(Z''_p)\text{-}\psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),

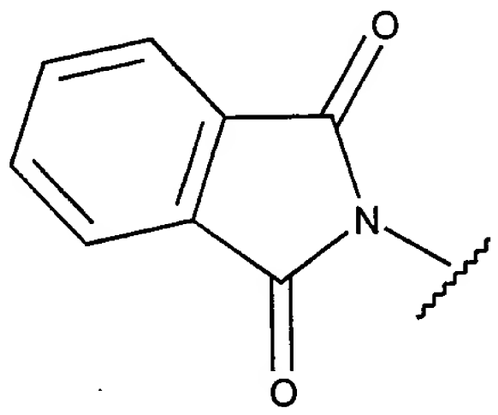
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R^1=Ø)



* biotin

- Z_k, Z'_k, and Z''_k can each represent and independently of one another:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ $-NHR_b$

6/ $-NH_2$

7/ $-NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

$-OR_b$

$-COOR_b$

$-CONHR_b$

$-CONH_2$

$-CH_2COOR_b$

$-CH_2CONHR_b$

$-CH_2CONH_2$

R_b representing an alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– $-\psi_k[*]-$ are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

$\psi_k[*]- = -CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; -NHCO -; -NHCONH- ; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF_k'-$; $-CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

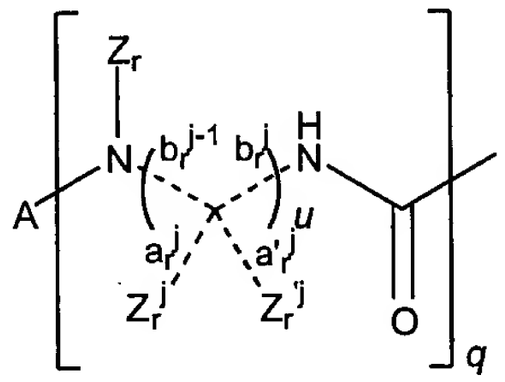
$A-N(Z_1)-C(Z'_1)(Z''_1)-CO-N(Z_2)-\ldots-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-\ldots CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-$

– "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above,

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: "j" takes all the whole values comprised from 2 to u+1,

– or "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are independently defined as previously for R^1, R^i, R'^i and R,

– the G group can be or contain:

A/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$-N(S_1)C(S'_1)(S''_1)-\Psi_1[*]-\ldots-\Psi_{k-1}[*]-C(S'_k)(S''_k)-\Psi_k[*]-\ldots\Psi_{h-1}[*]C(S'_h)(S''_h)-D$

– "k" is a whole number varying from 1 to h,

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– D can be:

hydrogen,

-COOH

$-COOR_c$

$-CONH_2$

$-CH_2COOR_c$

$-NHCOR_c$

$-CONR_cR_d'$

$-N(R_c)CON(R_d)$

-OH

$-OR_c$

-CN

$-C(O)R_c$

R_c and R_d representing independently of each other an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– or S_k, S'_k and S''_k can each represent independently:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ -CONHR$_e$

3/ -COOH

4/ -OH, OR$_e$

5/ -NHR$_e$

6/ -NH$_2$

7/ -NH(CO)R$_e$

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR$_e$ group

a NH$_2$ group

an OH group

a halogen

R$_e$ representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -Ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

-Ψ_k[*]- = -CH$_2$CH$_2$; -CH(F$_k$)=CH(F$_k$')- ; -CH$_2$NH- ; -NHCO- ; -NHCONH- ; -COCH$_2$- ; -CH(OH)CH$_2$- ; -CH(OH)CH$_2$NH- ; -CH$_2$- ; -CH(F$_k$)- ; -CH$_2$O- ; -CH$_2$-NHCONH- ; CH(F$_k$)NHCONF'$_k$- ; CH$_2$-CONH- ; CH(F$_k$)CONH- ; -CH(F$_k$)CH(F$_k$')CONH-

F$_k$ and F$_k$' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

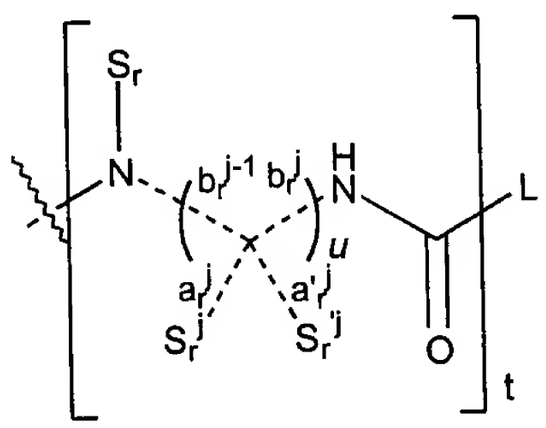
B/ an amino acid residue or an amino acid residue chain:

-N(S$_1$)C(S'$_1$)(S''$_1$)-CO-N(S$_2$)-…-CO-N(S$_k$)-C(S'$_k$)(S''$_k$)-CO-N(S$_{k+1}$)-…CO-N(S$_v$)-C(S'$_v$)(S''$_v$)-D

– "v" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10 with preferably v>3 and v>5,

– D, S_k, S'_k, and S''_k are independently defined as indicated above,

C/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds a_r^j, $a'_r{}^j$, b_r^j et b_r^{j-1} can also form a part of aromatic rings,

– the group L can be:

$-NH_2$

$-NHR_f$

$-NR_fR_g$

R_f and R_g representing, independently of each other, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_r, S_r^j, S'^j_r, can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and in the case of the proline the groups S_r and S'^j_r or S_r and S_r^j are linked together in order to give the proline cycle,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -OR_e

6/ -NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

-$COOR_e$

-$CONHR_e$

-$CONH_2$

-CH_2COOR_e

-CH_2CONHR_e

-CH_2CONH_2

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the X group represents a group giving to the compound of formula (V) an activated molecular structure adapted to react with alcohols or amines to form carbamates or ureas, and is particularly selected from phenols, if desired substituted with a nitro or a halogen or hydroxylamine derivatives and more particularly selected from:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compounds of formula (V) having the following property:

– if one or several asymmetric carbons are present in formula (V), then their configuration can be in independent manner either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i groups can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R'^i,

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

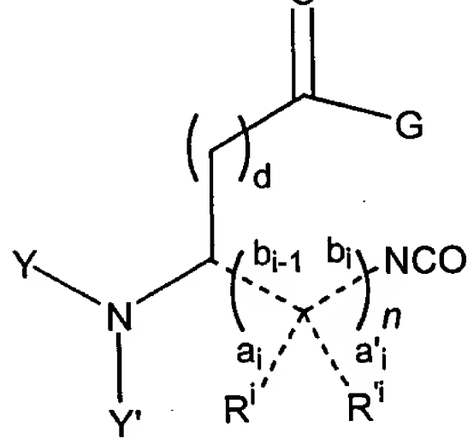
3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

and more particularly the compounds corresponding to formula (V) in which $1 \leq n \leq 4$, X = N-hydroxysuccinimide, A is an urethane or acyl group, and particularly

the compounds in which p, q, m, h, v and t are comprised from 1 to 10 and preferably equal to 1 or 2, and preferably those in which A = Boc and Fmoc.

The compounds of formula (V) are activated carbamates analogous to compounds of formulas (I) in which the activated carbamate is introduced into the side chain of a protected amino acid or a peptide, a pseudopeptide or else an oligomer of urea.

The invention also relates to compounds of formula (Vbis)



(Vbis)

in which

– "n" is a whole number greater than or equal to 1, comprised particularly from 1 to 4, and preferably from1 to 2,

– "d" is a whole number comprised from 0 to 4, preferably equaling 0 or 1,

– "i" is a whole parameter greater than or equal to 2 defined in the following manner: i takes all the whole values comprised from 2 to n+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_1 and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds can also form parts of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\Psi_1[*]\text{-}\ldots\text{-}\Psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\Psi_k[*]\text{-}\ldots\Psi_{p-1}[*]C(Z'_p)(Z''_p)\text{-}\Psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to p,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),

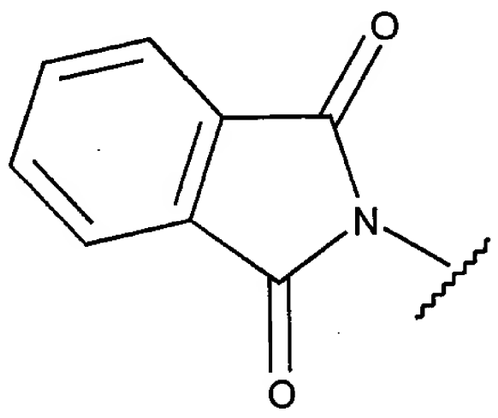
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R^1=Ø)



* biotin

– or Z_k, Z'_k, and Z''_k can each represent and independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

ψ_k[*]- = - -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F_k')$CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

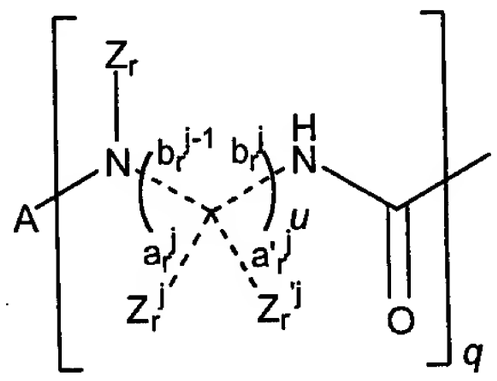
$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}CO\text{-}N(Z_2)\text{-}\ldots\text{-}CO\text{-}N(Z_k)\text{-}C(Z'_k)(Z''_k)\text{-}CO\text{-}N(Z_{k+1})\text{-}\ldots CO\text{-}N(Z_m)\text{-}C(Z'_m)(Z''_m)\text{-}CO\text{-}$

– "m" is a whole number greater than or equal to 1, preferably 1 to 50, preferably 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the integer values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and a'^j_r", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{n+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; a'^j_r and a'^{j+1}_r = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; a'^j_r and a'^{j+1}_r = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are defined as previously for R^1, R^i, R'^i, and R

– the group G can be or contain

A/ a pseudopeptide (peptide containing one or several pesudopeptide linkages)

$-N(S_1)C(S'_1)(S''_1)-\Psi_1[*]-\ldots-\Psi_{k-1}[*]-C(S'_k)(S''_k)-\Psi_k[*]-\ldots\Psi_{h-1}[*]C(S'_h)(S''_h)-D$

– "k" is a whole number varying from 1 to h,

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– D can be:

hydrogen,

-COOH

$-COOR_c$

$-CONH_2$

$-CH_2COOR_c$

-NHCOR

$-CONR_cR_d$

$-N(R_c)CON(R_d)$

-OH

$-OR_c$

-CN

$-C(O)R_c$

R_c and R_d representing independently of each other an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_k, S'_k and S''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -NHR_e

6/ -NH_2

7/ -$NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

a halogen

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

– -ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

ψ_k[*]- = - -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F_k')$CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

B/ an amino acid residue or a chain of amino acid residues:

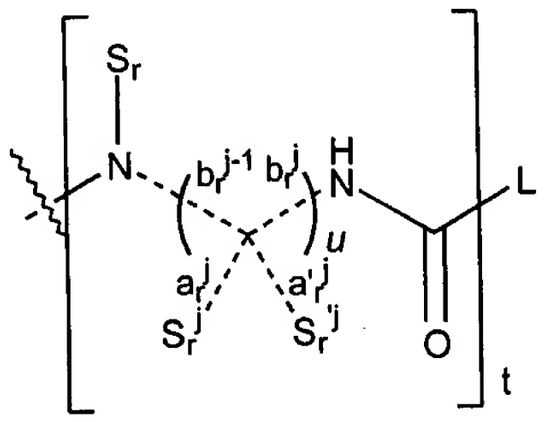
-$N(S_1)C(S'_1)(S''_1)$-CO-$N(S_2)$-…-CO-$N(S_k)$-$C(S'_k)(S''_k)$-CO-$N(S_{k+1})$-…CO-$N(S_v)$-$C(S'_v)(S''_v)$-D

– "v" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10 and preferably v>3 and v>5,

– "k" is a whole number varying from 1 to v,

– D, S_k, S'_k and S''_k are defined independently as above,

C/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds a_r^j, $a'_r{}^j$, b_r^j and b_r^{j-1} can also form a part of aromatic rings,

– the group L can be:

$-NH_2$

$-NHR_f$

$-NR_fR_g$

R_f and R_g representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_r, S_r^j, S'^j_r can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and, in the case of the proline, the groups S_r and S'^j_r or S_r and S_r^j are linked together in order to give the proline cycle,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ -COOH

4/ -OH

5/ $-OR_e$

6/ NHR_e

7/ $-NH_2$

8/ $-NH(CO)R_e$

9/ aryl whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

$-COOR_e$

$-CONHR_e$

$-CONH_2$

$-CH_2COOR_e$

$-CH_2CONHR_e$

$-CH_2CONH_2$

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

the compounds of formula (Vbis) having the following property:

– if one or several asymmetric carbon atoms are present in formula (V), then their configuration can be independently of each other either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations as follows:

1/ cyclization between R^i and R'^i

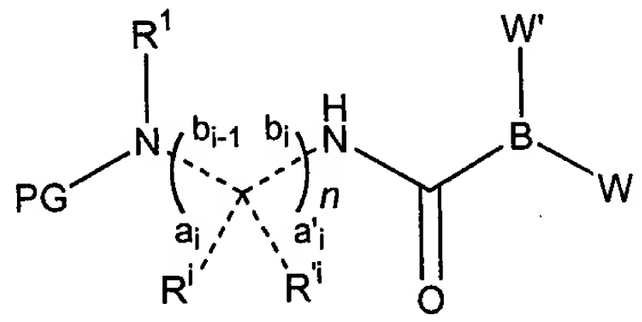
2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

and more particularly the compounds having the formula (Vbis) in which $1 \leq n \leq 4$, X = N-hydroxysuccinimide and A is an urethane or acyl group, and particularly the compounds in which p, q, m, h, v and t are comprised from 1 to 10 and preferably equal to 1 or 2, and preferably those in which A = Boc and Fmoc.

The isocyanates of formula (Vbis) can be used as precursors for the synthesis of compounds of formula (V) and can be obtained from compounds (XI).

The invention also relates to compounds of formula (VI)



(VI)

in which

– "n" is a whole number greater than or equal to 1, comprised particularly from 1 to 50, and preferably from 1 to 10,

– "i" is a whole number varying from 2 to m+1,

– a_i and a'_i, represented by a broken line, are covalent bonds which can be single (s) or double (d),

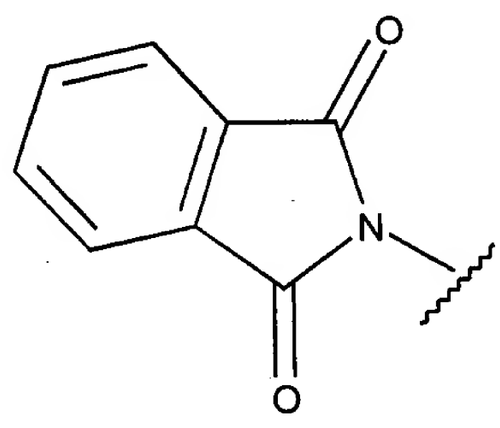
"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_1 and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds can also form parts of aromatic rings,

– GP is a protective group selected from:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
* aryl, particularly phenyl,
* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,
* phthalimide (R^1=Ø)



* O_2 (corresponds to a nitro group as masked form of the amine), R^1 = Ø

– the R_1, R_i, R'_i and R groups can each represent independently of each other: hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the B group can be N or O,

– the W and W' groups can be or contain:

A/ hydrogen

B/ a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_h$

2/ -$CONHR_h$

3/ -COOH

4/ -OH

5/ -OR_h

6/ -NHR

7/ -NH_2

8/ -$NH(CO)R_h$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_h representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

C/ an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

D/ a side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, and in the case of proline, W = W' = -CH_2-CH_2-CH_2-CH(COOR)-)

E/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

-$C(S'_1)(S''_1)$-Ψ_1[*]-...- Ψ_{k-1}[*] (S_k)-$C(S'_k)(S''_k)$-Ψ_k[*]-...Ψ_{h-1}[*]$C(S'_h)(S''_h)$-D

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to h,

– D can be:

hydrogen,

-COOH

-$COOR_c$

-$CONH_2$

-CH_2COOR_c

-$NHCOR_c$

-$CONR'_cR'_d$

-$N(R_c)CON(R_d)$

-OH

-OR_c

-CN

-$C(O)R_c$

R_c and R_d representing independently of each other an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_k, S'_k and S''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -NHR_e

6/ -NH_2

7/ -$NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

a halogen

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

– $-\psi_k[*]-$ are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

$\psi_k[*]-$ = $-CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; $-NHCO-$; $-NHCONH-$; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF_k'-$; $CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

F/ an amino acid residue or an amino acid residue chain:

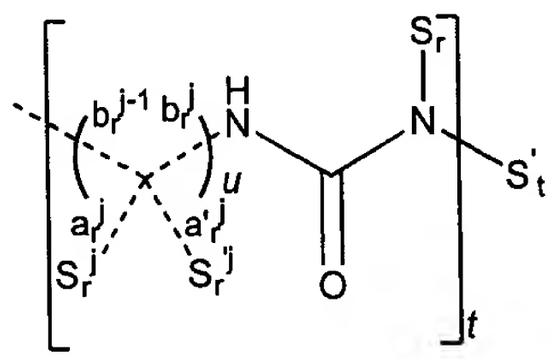
$-C(S'_1)(S''_1)-CO-N(S_2)-\ldots-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-\ldots CO-N(S_v)-C(S'_v)(S''_v)-D$

– "v" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10, with preferably v>3 and v>5,

– "k" is a whole number varying from 1 to v,

– D, S_k, S'_k, and S''_k are independently defined as indicated above,

G/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– S_r, S_r^j, $S'_r{}^j$, S'_v can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and in the case of proline ($S_r^j = S'_r{}^j$ = -CH_2-CH_2-CH_2-CH(COOR)-),

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -OR_e

6/ -NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

$-COOR_e$

$-CONHR_e$

$-CONH_2$

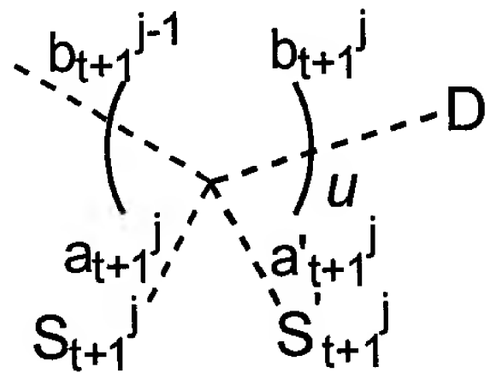
$-CH_2COOR_e$

$-CH_2CONHR_e$

$-CH_2CONH_2$

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

S'_t can also represent the group defined by the following formula:



S_{t+1}^j, S'^j_{t+1} having the meanings as indicated for S_r, S_r^j, S'^j_r and S'_v,

D, u have the same meanings as indicated above,

– "a^j_{t+1} and a'^j_{t+1}", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_{t+1}^{j-1} and b_{t+1}^{j}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_{t+1}^j and b_{t+1}^{u+1} are always single bonds (s),
* if $b_{t+1}^j = d$, then a_{t+1}^j and $a_{t+1}^{j+1} = s$; a'^j_{t+1} and $a'^{j+1}_{t+1} = \emptyset$; b_{t+1}^{j-1} and $b_r^{j+1} = s$
* if $b_{t+1}^j = t$, then a_{t+1}^j and $a_{t+1}^{j+1} = \emptyset$; a'^j_{t+1} and $a'^{j+1}_{t+1} = \emptyset$; b_{t+1}^{j+1} and $b_r^{j-1} = s$
* if $a_{t+1}^j = d$, then b_{t+1}^{j-1} and $b_{t+1}^j = s$,

the compounds of formula (VI) having the following property:

– if one or several asymmetric carbon atoms are present in formula (VI), then their configuration can be independently of each other either R (rectus) or S (sinister),

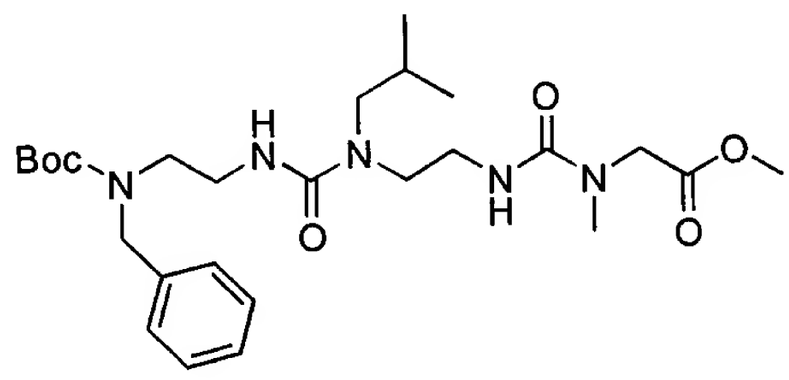
– the groups R_1, R_i, R'_i can also be defined on the basis of intramolecular cyclizations as follows:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

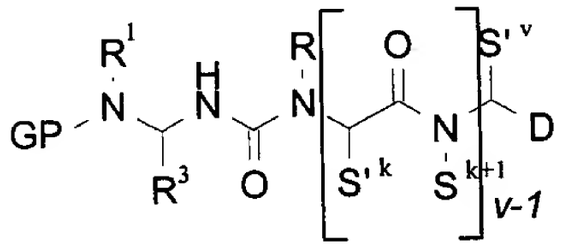
provided that the compound of formula (VI) is different from:



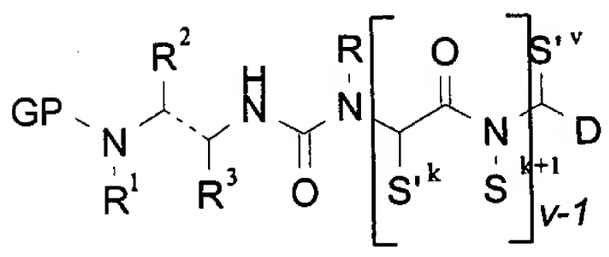
The isocyanates of formula (VI) are reaction products of compounds of type (I) or possibly (II) with derivatives containing a primary or secondary amine or an alcohol.

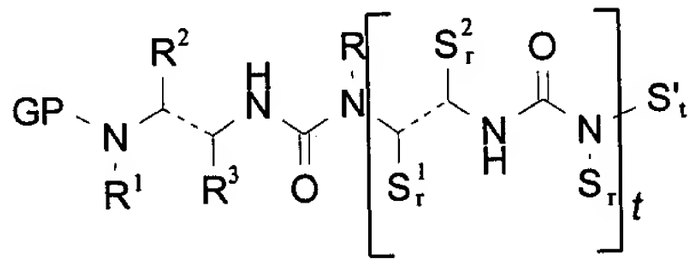
A group of advantageous compounds is constituted by those of formula (VI) in which $1 \leq n \leq 4$, and GP is an urethane or acyl group defined according to claim 12, and more particularly the following compounds for which v, and t are comprised from 1 to 10, and preferably equal to 1 or 2, and particularly those for which GP = Boc and Fmoc and O_2:

n=1

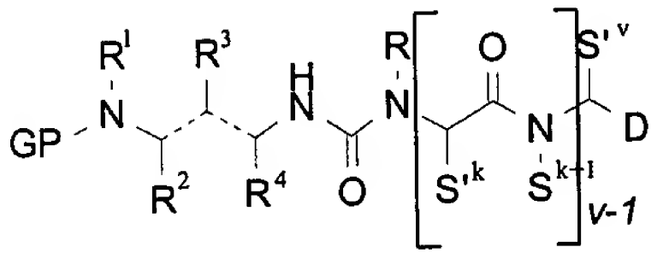


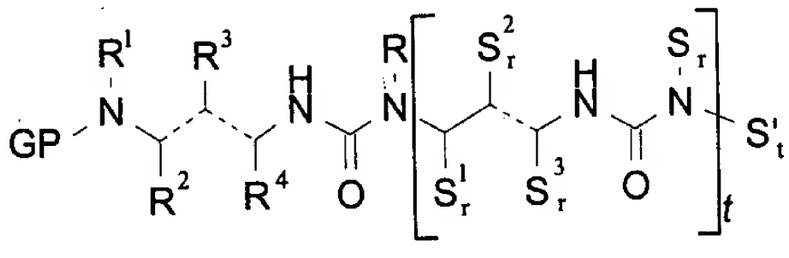
n=2



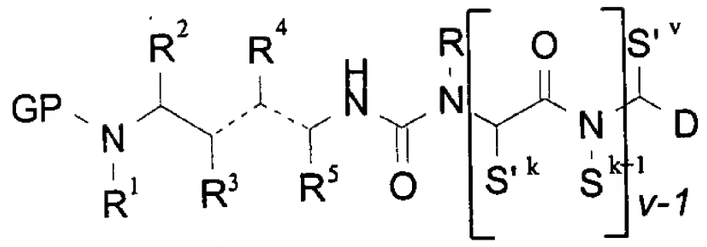


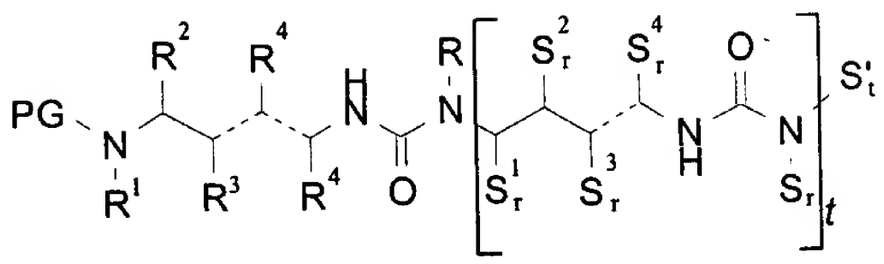
n=3

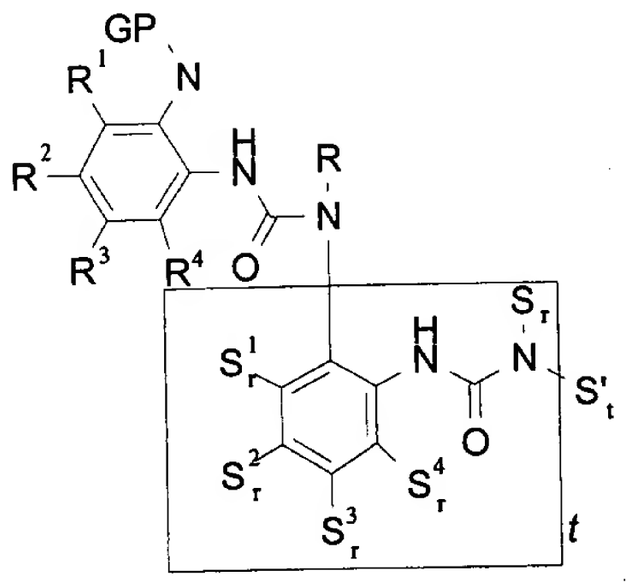


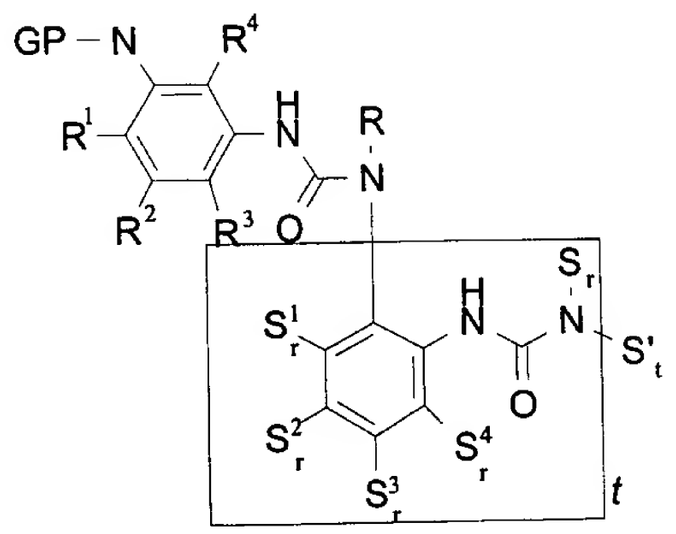


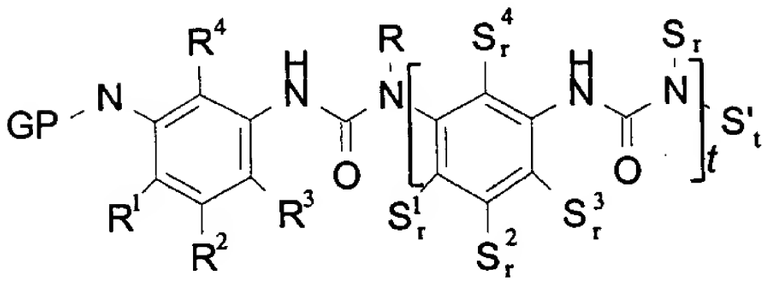
n=4

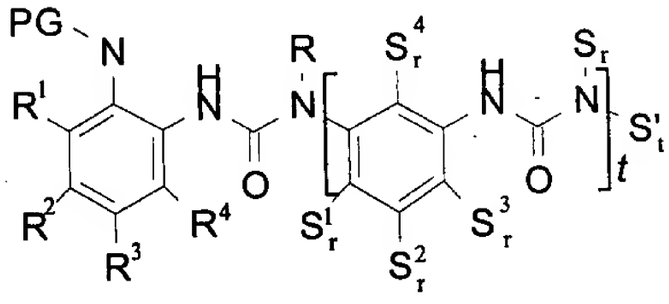






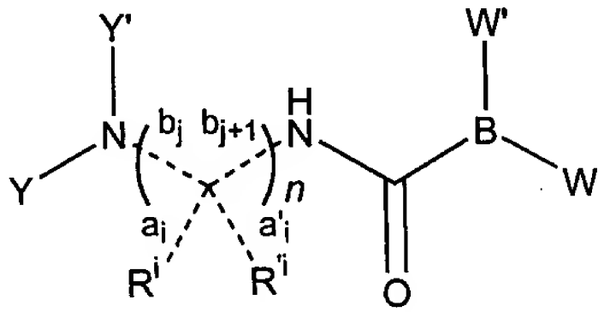






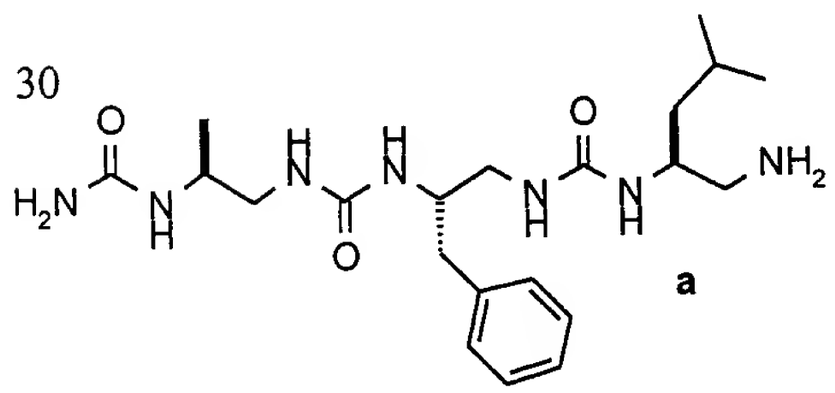
the broken lines corresponding to single or double bonds, with proviso that two double binds are not contiguous.

The invention also relates to compounds of formula (VII)

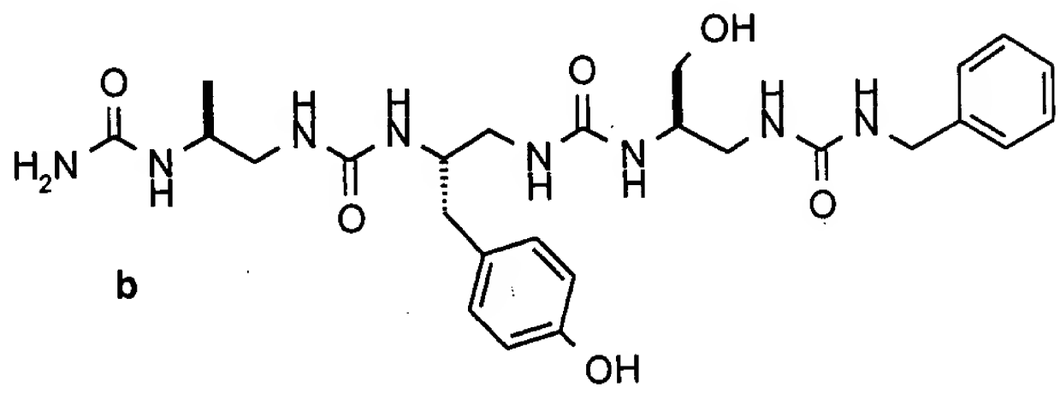


(VII)

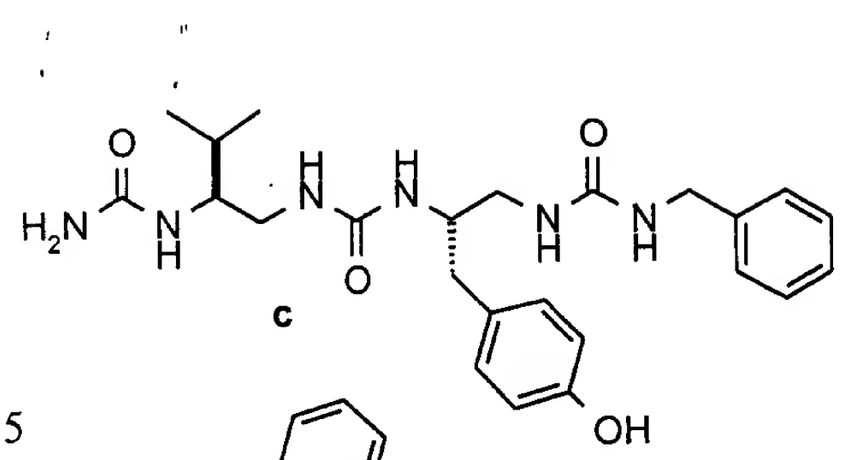
in which Y, Y', R^i, R'^i, B, W, W', a_i, a'_i, b_j, b_{j+1} have the meanings as indicated above, provided that the compounds of following formulas are excluded:



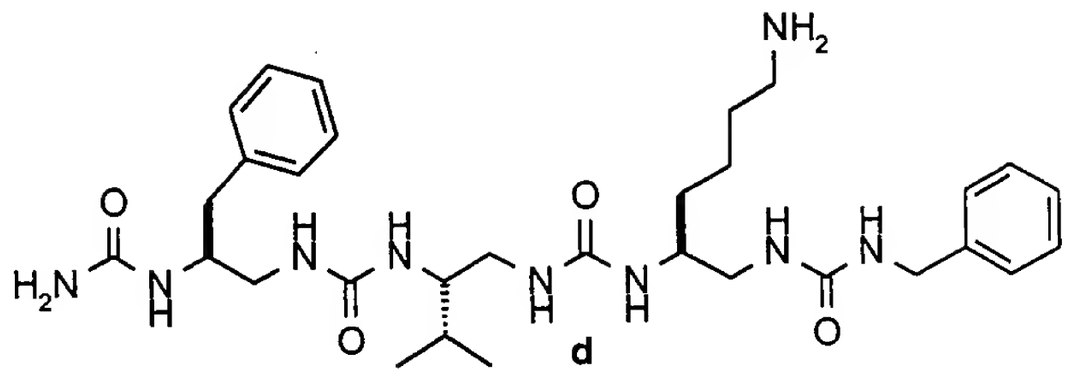
a



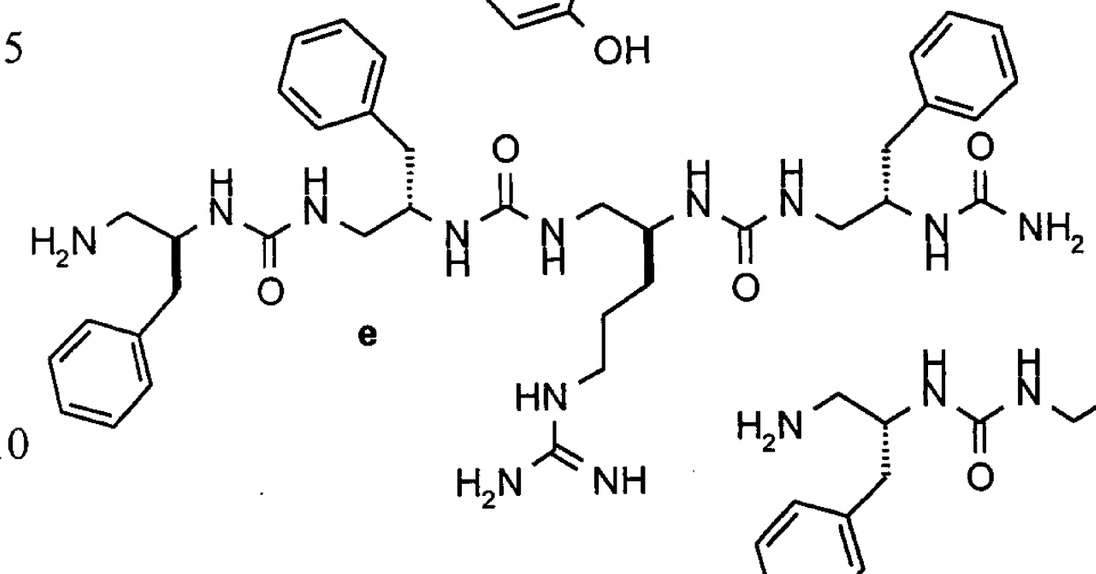
b



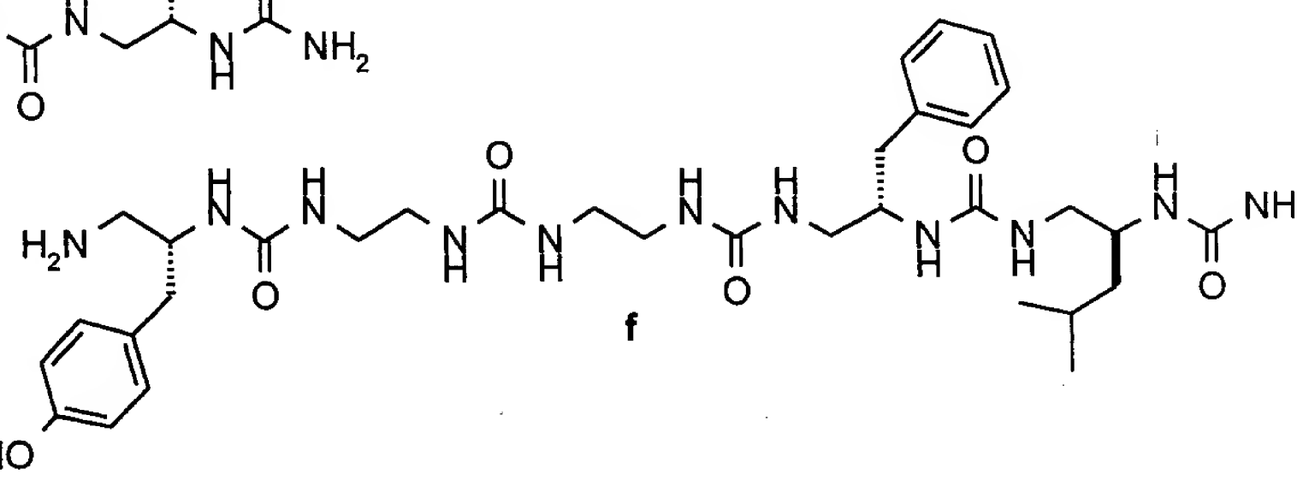
c



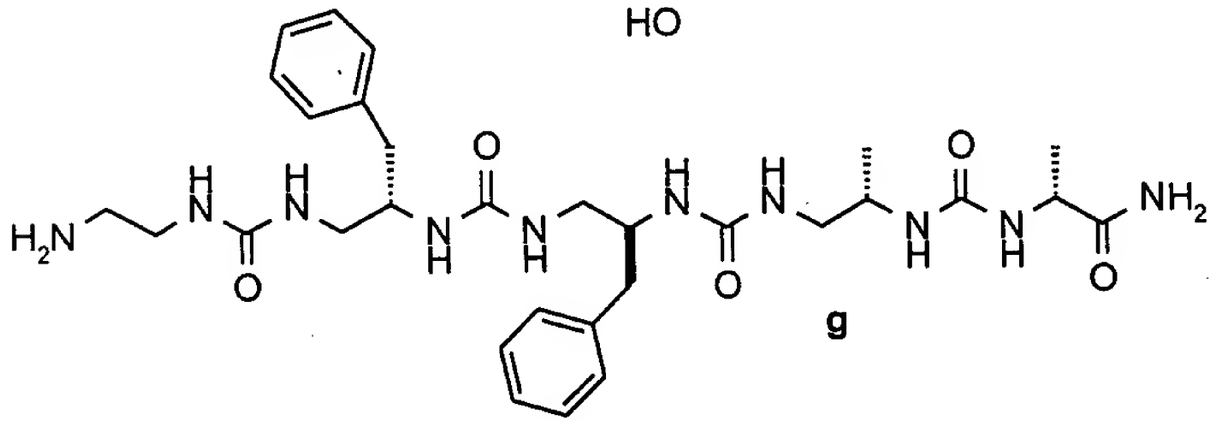
d



e

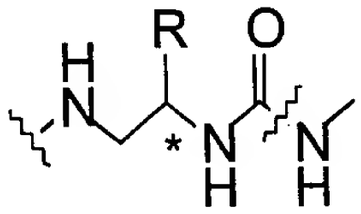


f



g

and provided that the compound of formula (VII) is different from the analogs of the peptide Tyr-Gly-Gly-Phe-Leu-OH, containing one or several derivatives as defined below mimicking the side chain of the amino acids present in the peptide and permitting the introduction of one or several urea linkages, which is to say the compound of formula (VII) is different from the following compounds:



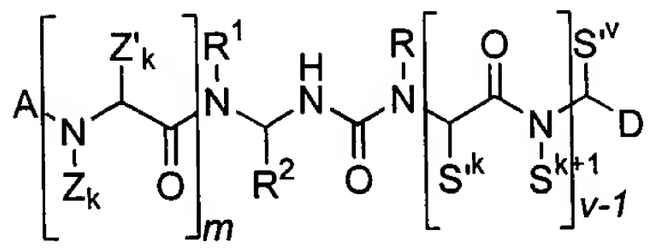
in which R represents hydroxybenzyl, a hydrogen atom, a benzyl group, or an isobutyl group.

The compounds of type (VII) are reaction products of compounds of type (III) and (III) or possibly (IV) with derivatives containing a primary or secondary amine or an alcohol.

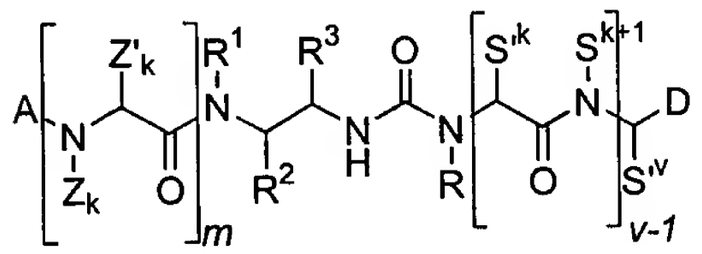
An advantageous group of compounds of formula (VII) is constituted by those in which $1 \leq n \leq 4$, , and particularly the following compounds for which v, t, m and q are

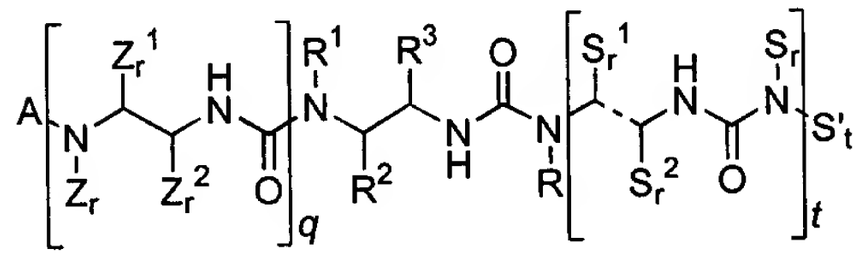
comprised from 1 to 10, and preferably from 1 to 5, and more particularly the following compounds:

n=1

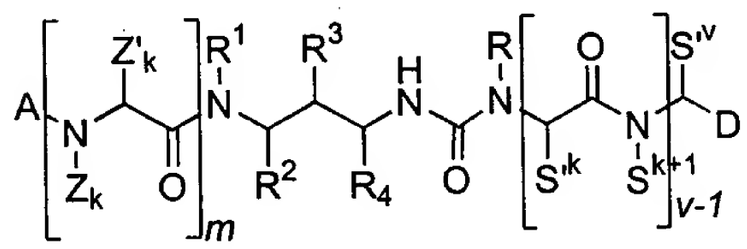


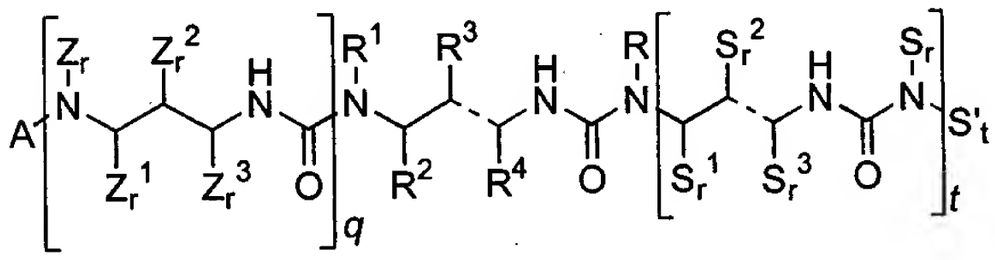
n=2



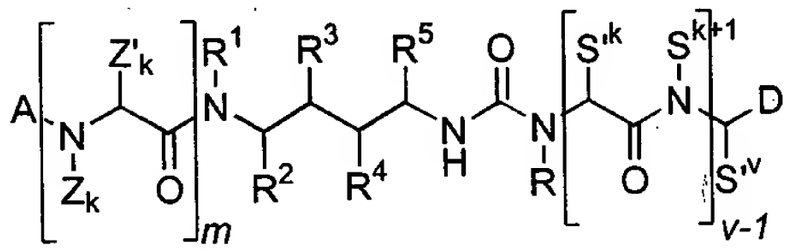


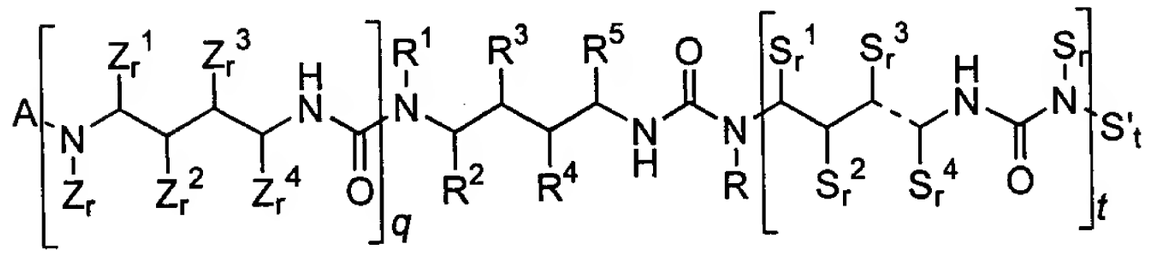
n=3



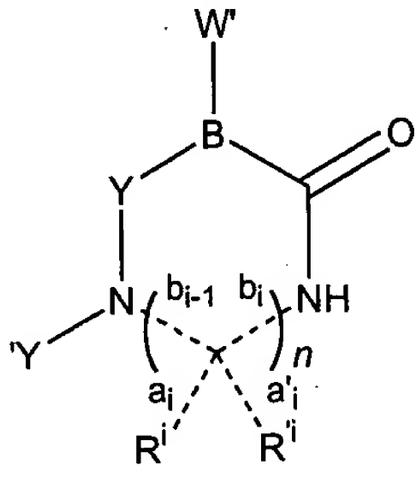


n=4





The invention also relates to compounds of the formula (VIII)



(VIII)

in which:

the total number of atoms forming the cycle is greater than seven,

the groups R_i, R'_i, Y', W', B have the meanings already indicated above,

the group Y in this new case can be or contain:

I/ a (C1-C20) alkyl group, unsubstituted or substituted with one or more substituents from the following:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -OR

6/ -NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms,

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

II/ an aryl group

III/ a pseudopeptide (peptide containing one or several pseudopeptidic linkages)

(on B←) -$C(Z'_1)(Z''_1)$-ψ_1[*]-…-ψ_{k-1}[*] (Z_k)-$C(Z'_k)(Z''_k)$-ψ_k[*]-…ψ_{p-1}[*]$C(Z'_p)(Z''_p)$-CO-(→ on NY')

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– Z_k, Z'_k and Z''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic or non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -ψ_k[*]- are independently either CO-NH peptidic linkages or linkages of different chemical natures selected particularly from the following list:

-ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$-; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F'_k)$CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

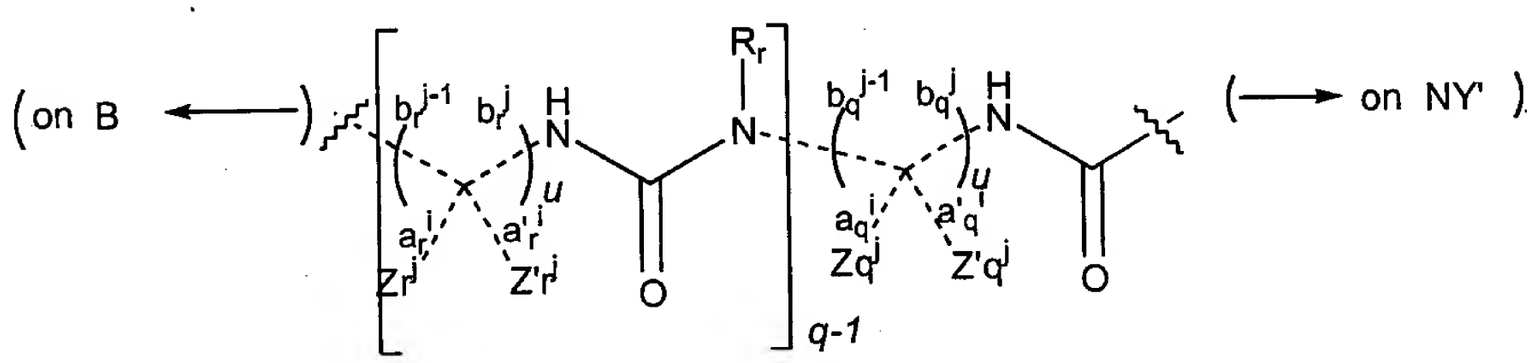
IV/ an amino acid residue or a chain of amino acid residues:

(on B←)-C(Z'_1)(Z''_1)-CO-N(Z_2)-…-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-…CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-(→ on NY')

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– Z_k, Z'_k, and Z''_k are defined as above,

V/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter comprised between 2 and u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q-1,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s), or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

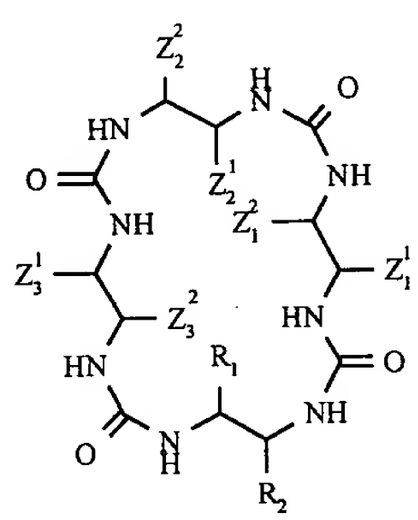
* $b_q{}^1$ and $b_q{}^{u+1}$ are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

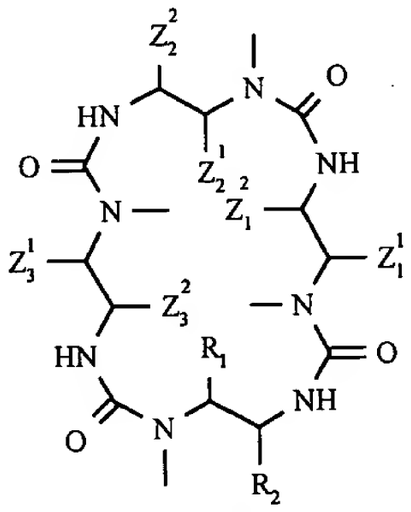
certain of these bonds can also form a part of aromatic rings,

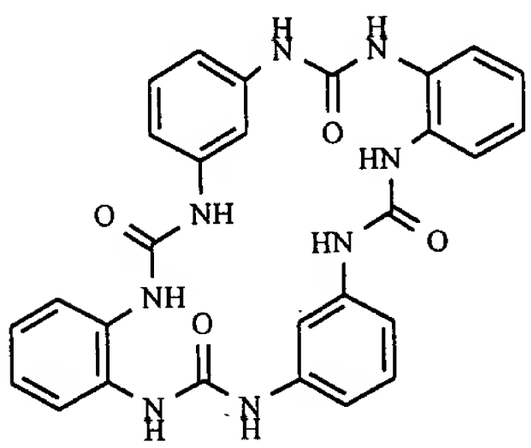
– Z_r, Z_r^j, $Z'_r{}^j$ have the meanings indicated with respect to R^1, R^i, R''^i as defined above.

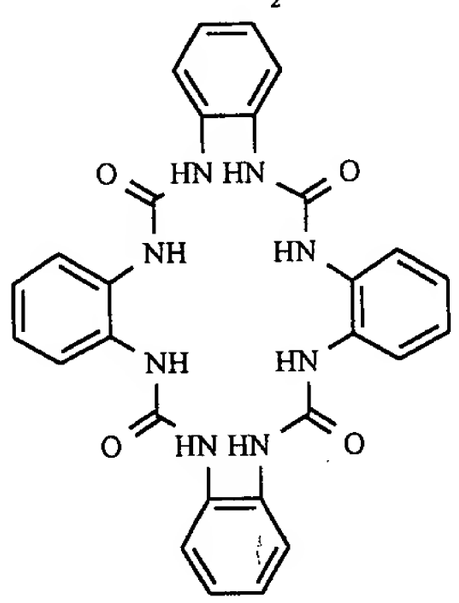
The compounds of the (VIII) type are cyclic compounds obtained from compounds of the (III) or (IV) type and by intramolecular reaction with an amine liberated after elimination of temporary protection.

A preferred group of compounds of formula (VIII) is constituted by those in which $1 \leq n \leq 4$, and particularly the following compounds in which h, v, t, p, m, and q are comprised from 1 to 10 and preferably from 1 to 5, and more particularly the following compounds:









in which R^1 and R^2 have the meanings indicated above and in which $Z_1{}^1$, $Z_1{}^2$, $Z_2{}^1$, $Z_2{}^2$, $Z_3{}^1$ and $Z_3{}^2$ have the meanings indicated with respect to Z_r^j.

In the compounds of formula (III), (IV), (V), (Vbis), (VI) and (VII), the aryl group is preferably selected from:

1/ phenyl

2/ naphthyl

3/ indenyl

4/ thiophenyl

5/ benzothiophenyl

6/ furanyl

7/ benzofuranyl

8/ pyridyl

9/ indolyl

10/ pyrollyl

or the aryl group non substituted or substituted with 1 to 6 substituents selected particularly from:

1/ alkyl of 1 to 10 carbon atoms

2/ halogen

3/ alkoxy of 1 to 10 carbon atoms

4/ hydroxyl

5/ amine of 1 to 10 carbon atoms

6/ ester of 1 to 10 carbon atoms

7/ nitrile

8/ aryl, whose cycle structure contains 5 to 20 carbon atoms

9/ nitro

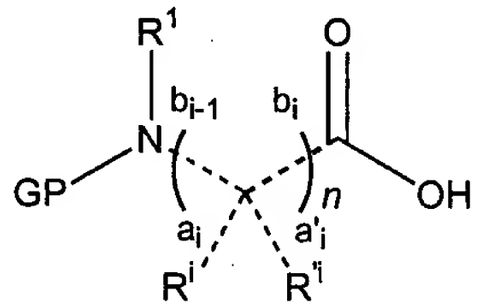
10/ urea of 1 to 10 carbon atoms

11/ amide of 1 to 10 carbon atoms

12/ guanidine.

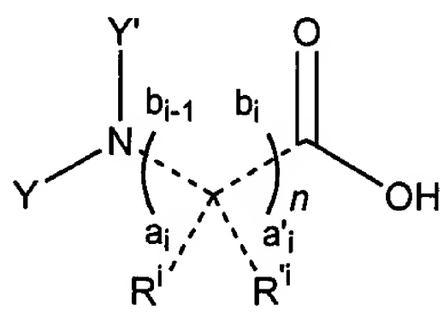
The compounds of formula (I), (II), (III), (IV), (V) or (V bis) can be prepared according to the following process from respectively:

– compounds of formula (IX) (for compounds of formula (I) and (II))



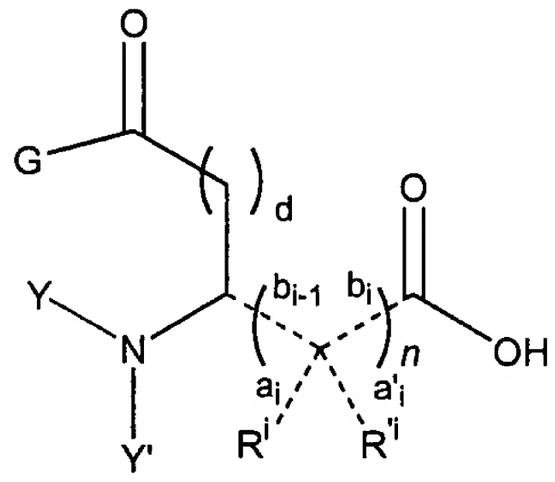
(IX)

– compounds of formula (X) (for compounds of formula (III) and (IV))



(X)

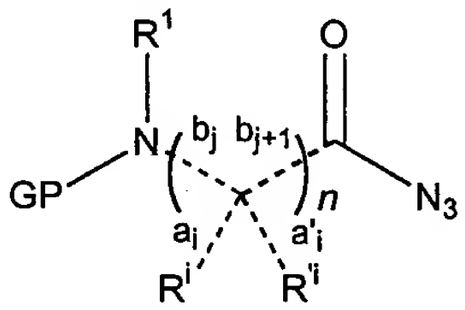
– compounds of formula (XI) (for compounds of formula (V) and (V bis))



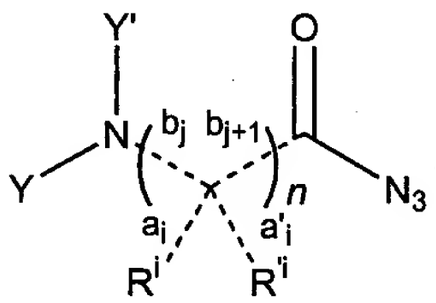
(XI)

comprising

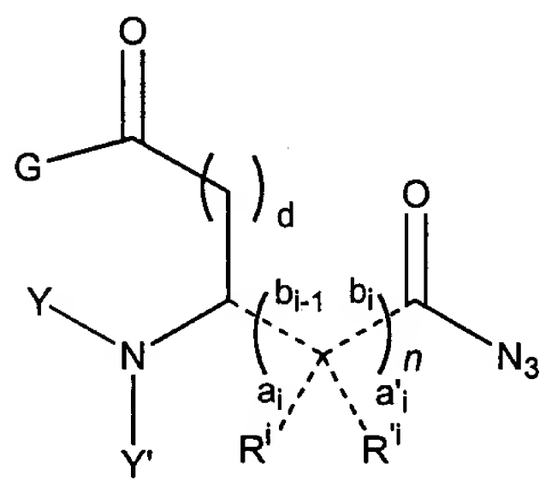
(a) a step of transformation of the acid (IX) or (X) or (XI) into a corresponding acyl azide (XII) or (XIII) or (XIV) respectively,



(XII)



(XIII)



(XIV)

for example by treatment of the mixed anhydride (formed by reaction of acid (IX), (X) or (XI) with ethyl or isobutyl chloroformate in the presence of a tertiary amine such as NMM (N-methylmorpholine), DIEA (di-isopropylethylamine) or Et_3N in THF (tetrahydrofurane at -15°C)) with a sodium azide solution,

(b) a step of transformation of the acyl azide (XII) or (XIII) or (XIV) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) or (Vbis), respectively,

for example by heating a solution of the acyl azide in a suitable solvent, particularly toluene or xylene (for example at 65°C), the formation of the isocyanate being liable to be followed by observation of the release of gas into the balloon, the end of the gaseous emission signifying completion of the Curtius rearrangement,

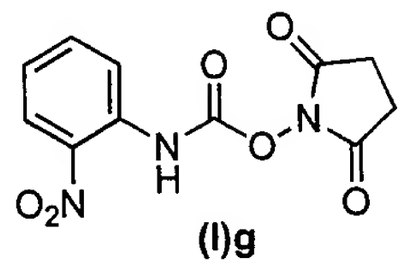
(c) a step of treatment of the isocyanate (II), (IV) or (V bis), preferably not isolated, the isocyanate being in solution, for example in hot toluene (at 65°C for example), with one of the derivatives from the following list:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- imidazole
- tetrazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

(permitting obtaining a pre-activated synthon) and if desired a base such as pyridine, to obtain a carbamate of formula (I), (III) or (V), which is then advantageously isolated, preferably by crystallization or by purification, particularly on a silica column, or by HPLC or by aqueous, acid or basic washing after dissolution in an organic solvent.

The compounds of formula (VI), (VII) or (VIII) can be prepared according to the process comprising the reaction of compounds containing primary or secondary amines, with one of the products of formula (I), (II), (III), (IV), (V) or (Vbis) defined above, for example in a solvent such as DMF, H_2O/acetone, THF or dichloromethane with or without the addition of a base such as Et_3N, DIEA, NMM, Na_2CO_3.

Figure 1: Figure 1 corresponds to the X-ray structure of the carbamate (**Ig**) corresponding to the following formula:



(I)g

The invention is illustrated hereafter by examples I and II, which have no limiting value.

In example I, the reaction of the *O*-succinimidyl-2-(*tert*-butoxycarbonylamino)-ethylcarbamate derivatives with aliphatic or aromatic primary amines, secondary amines, or α- or β-amino acid derivatives, rapidly gives the expected urea derivatives or urea oligomers with a high yield. In example II, the *O*-succinimidyl-2-[(*9H*-fluoren-9-ylmethoxy)carbonylamino]-ethylcarbamate derivatives used in a repetitive manner in solid phase permit obtaining the desired urea pseudopeptides and urea oligomers, with a high yield.

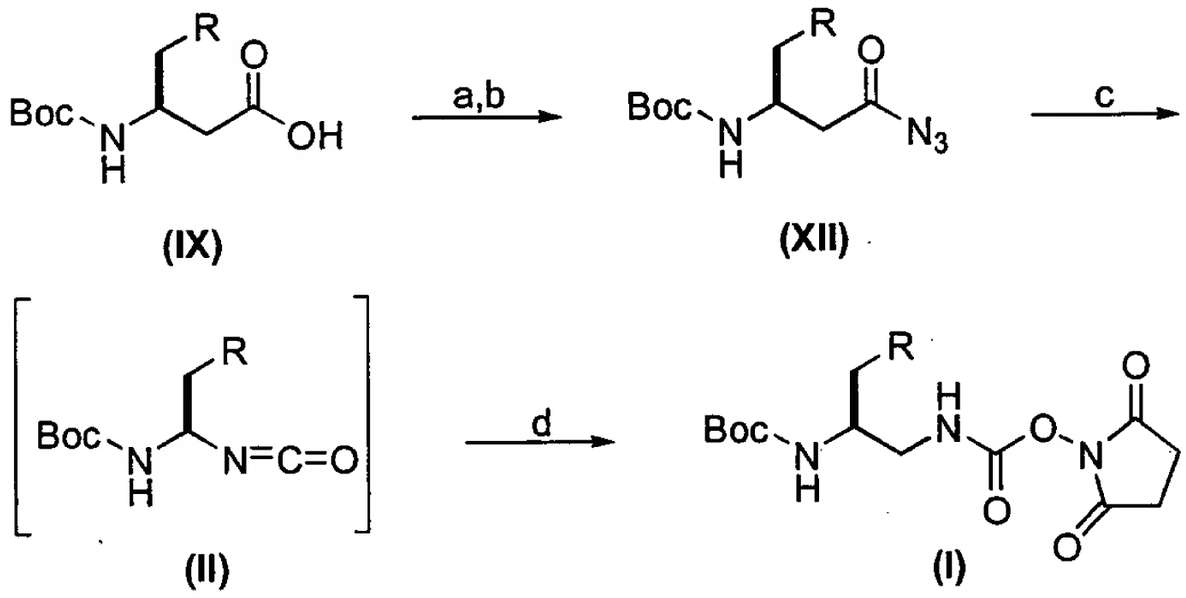
EXAMPLE I

An efficacious synthesis of *O*-succinimidyl-2-(*tert*-Butoxycarbonylamino)-ethylcarbamate derivatives (I) is described as well as their utilization as activated monomers in the synthesis of di- and tri-substituted ureas and urea oligomers. The *β*-amino *N*-Boc-protected acids (IX) are first transformed into the corresponding acyl azide derivatives (XII). The isocyanate formed by Curtius rearrangement of compounds (XII) is immediately treated with N-hydroxysuccinimide in the presence of pyridin to give the corresponding carbamates (I)(see the formula of reaction 1) (50-64%). These carbamates are stable and crystalline compounds which react spontaneously with primary and secondary amines at ambient temperature to give (VIe) ureas (79-87%). By way of example, the synthesis of the N-boc-protected tri-urea derivative (VIg) has also been carried out by step-by-step elongation using carbamate (Ib).

The *N*-Boc-protected *β*-amino acids (IX) are first transformed into the corresponding acyl azides (XII) by reaction of their mixed anhydride (prepared with EtOCOCl/N-methylmorpholine) with NaN_3. The isocyanates (II), generated *in situ* by heating the acyl azide (XII) in toluene at 65° are immediately treated with N-

hydroxysuccinimide (1 equivalent) in the presence of pyridine (1 equivalent) to give the carbamate (I). This sequence of reaction from (IX) is generally complete in less than one hour (reaction 1).

Reaction 1



(IX) (XII) (II) (I)

Reagents: (a) i-BuOCOCl, NMM, -20°C; (b) NaN_3, H_2O; (c) Toluene, 65°C; (d) N-hydroxysuccinimide, pyridine.

The *O*-succinimidyl carbamates (I) crystallize for the most part directly from the solution of toluene at ambient temperature and are obtained simply by filtration with suitable yield. Recrystallization in toluene or another suitable solvent permits obtaining pure specimens for analysis. It is interesting to note that the mild conditions employed are compatible with the use of functionalized side chains (Table 1).

Table 1. Conversion of β-amino acids (IX) into O-succinimidyl carbamates (I).

R =	Products (I)	Yield (%)[a]	m.p. (°C)	HPLC t_R (min)[b]
H	Ia	55	132-134	6.95
Me	Ib	60	153-155	8.00
i-Pr	Ic	51	125-127	10.80
Bn	Id	55	163-164	12.79
$CH_2CO_2(Bzl)$	Ie	58	115-117	13.47
CH(Me)OBzl	If	64	109-110	14.59

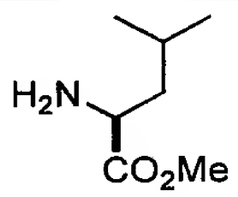
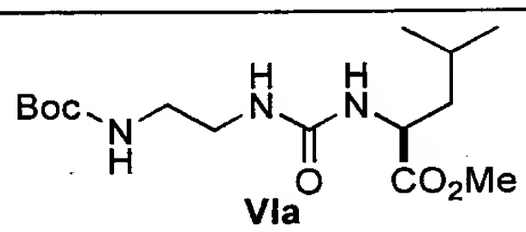
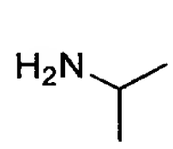
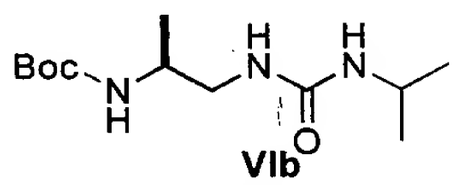
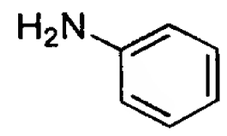
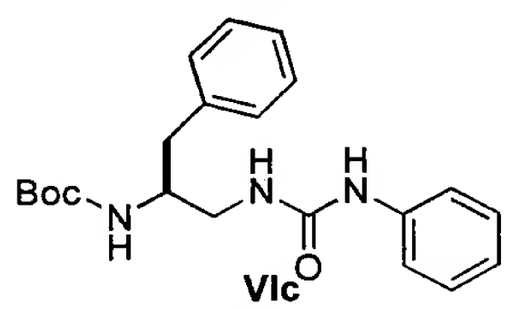
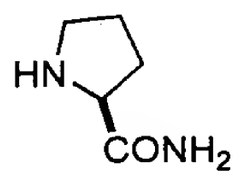
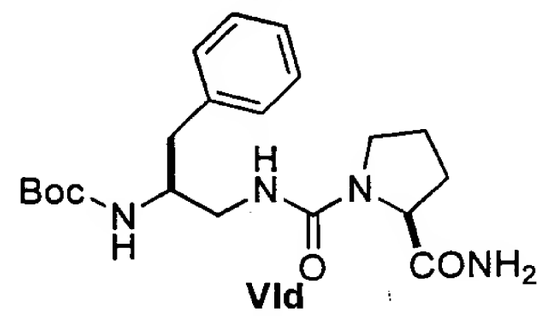
[a]Yield of (I) after recrystallization. [b]linear gradient of A (0.1% CF_3COOH in H_2O) and B (MeCN containing 0.08% CF_3COOH), 20-80% B, 20 min. The compound of formula (**I**) is that indicated in reaction 1 above.

Starting with 2-nitrobenzoic acid[8], the corresponding O-succinimidyl carbamate (Ig) has been isolated with 71% yield after recrystallization in ethyl acetate. The X-ray structure of the carbamate (Ig)(Figure 1) shows that the molecule has an extended configuration with an intra-molecular hydrogen bond between the adjacent nitro and carbamate groups ($N_2 \ldots O_2$, 2.62 Å). The succinimidyl cycle is turned about 77° relative to the plane of the phenyl cycle.

Carbamates (I) and (Ig) are stable crystalline solids which can be stored for months at 4°C without degradation. So as to study the possibilities and limits of the activated monomers of the invention for the preparation of substituted symmetric ureas, different amines and amino acids have been treated with the carbamates (I). The results are shown in Table 2.

Table 2

Formation of substituted ureas (VI) with carbamates (I)

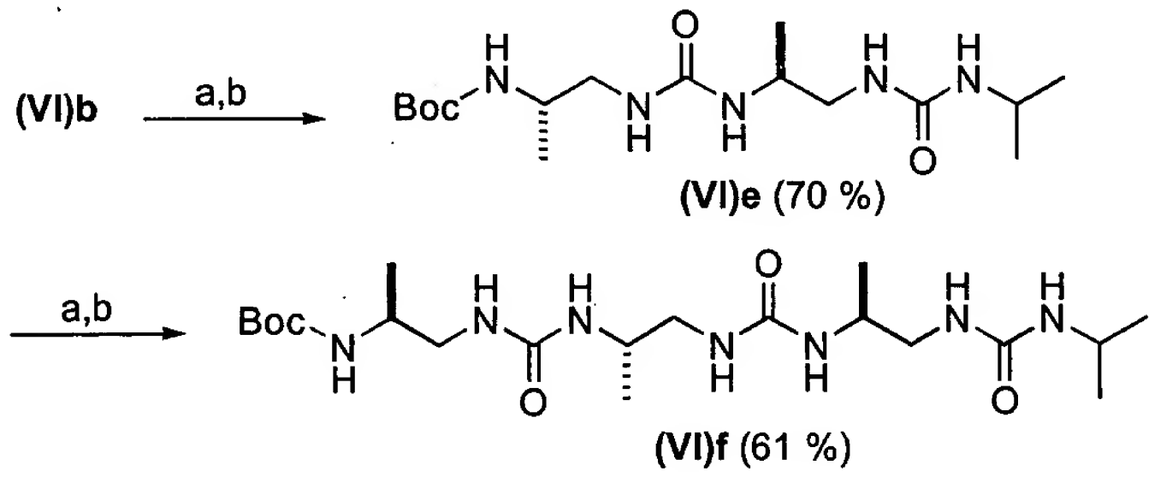
Entry	Carbamate	Amine	Time (min)[a]	Urea **VI**	Yield(%)[b]
1	**Ia**		20	 **VIa**	78
2	**Ib**		20	 **VIb**	85
3	**Id**		20	 **VIc**	87
4	**Id**		30	 **VId**	89

[a] Reaction conditions: carbamate (3 mmol), amine (3-4 mmol), Hunig base (3 mmol), DMF (5 ml), ta.[b] yield after purification.

It is found that the carbamates (I) react with primary amines or amino acids in the presence of Hunig base at ambient temperature to give the corresponding urea derivatives (VI) with good yield (table 1, entry 1, 2). The reaction is very rapid and all the initial product is generally consumed in twenty minutes. The N-hydroxysuccinimide is the only secondary product formed during the reaction and is easily eliminated by aqueous washing. Under the same conditions, the aromatic amines such as aniline (entry 3) and a secondary amine (entry 4) also rapidly react with the carbamate (Id) to give the ureas (VIc) and (VId) respectively.

The repetitive formation of urea by using carbamates (I) as activated monomers permits obtaining urea oligomers as shown by the synthesis of Boc-$A^{u}CH_2$-$A^{u}CH_2$-*i*-Pr (VIe) and Boc-$A^{u}CH_2$-$A^{u}CH_2$-$A^{u}CH_2$-*i*-Pr (VIf). (reaction 2).[9]

Reaction 2



Reagents (a) TFA; (b) (Ib), Hunig base, DMF.

In conclusion, the *O*-succinimidyl-*β*-(*tert*-butoxycarbonylamino)-carbamates (I) are easily prepared from *β*-amino acids and react properly and with good yield with the primary and secondary amines to form urea derivatives. The mild conditions employed for the preparation of carbamates (I) are compatible with most of the side chains of the natural amino acids and these stable intermediaries represent synthons attractive for the synthesis in solid phase of urea peptides and urea oligomers.

Experimental Section

Generalities. The amino acid derivatives have been bought from Neosystem or Novabiochem. THF is distilled with Na/benzophenone under argon before use. The toluene is distilled over P_2O_5 and preserved on a 4Å molecular sieve. The aniline was passed through an alumina column before use. The Boc-β^3-amino acids were prepared according to procedures of the literature[10] by Arndt-Eistert homologation of the

commercial protected amino acids. Reactions were conducted under argon pressure. The HPLC analysis was carried out on a Nucleosil C_{18} column (5 m, 3.9 x 150 mm) by using a linear gradient of A (0.1% CF_3COOH in H_2O) and B (MeCN) at a flow rate of 1.2 ml/min with UV detection at 214 nm.

General procedure for the preparation of *O*-succinimidyl carbamates (I). The N-protected β-amino acid (10 mmol) is dissolved in THF (30 ml) under argon and cooled to -20°. After addition of *i*-BuOCOCl (11 mmol) and NMM (11 mmol, 1.1 equivalent), the reaction mixture is agitated at -20° for 20 minutes. The resulting white suspension is reheated to -5°, and is treated with a 5 ml solution of NaN_3 (25 mmol). The mixture is then agitated for 5 minutes, diluted with EtOAc, washed with saturated NaCl, dried on $MgSO_4$ and concentrated under reduced pressure to give the acyl azide (XI) which is used without further purification. The toluene is then added under argon and the resulting solution is heated to 65°C with agitation. Once the emission of gas has stopped (about 10 minutes), the *N*-hydroxysuccinimide (10 mmol) and the pyridine (10 mmol) are added. The mixture is agitated for 5 minutes at 65°C and cooled to ambient temperature. In most cases, the desired product crystallizes in the toluene solution and is collected by filtration. Recrystallization in toluene permits obtaining pure *O*-succinimidyl carbamate. Otherwise, the solvent is evaporated under vacuum and the residue is purified by recrystallization in the suitable solvent.

***O*-succinimidyl-2-(*tert*-Butoxycarbonylamino)ethylcarbamate (Ia).** 3-(*tert*-butoxycarbonylamino)propanoic acid (3.78 g, 20 mmol) is transformed by following the general procedure. A recrystallization in toluene gives the compound (Ia)(3.3g, 50%), constituted by colorless crystals; mp. 132-134°C; HPLC t_R 6.95 minutes (linear gradient, 20-80% B, 20 minutes); ^{1}H-NMR (200 MHz, DMSO-D_6): 1.38 (s, 9H), 2.76 (s, 4H), 3.00-3.11 (m, 4H), 3.78-3.93 (m, 1H), 6.87 (br t, 1H); 8.27 (t, J = 5.1 Hz, 1H). ^{13}C-NMR (50 MHz, CD_3CN): 171.7, 157.5, 153.1, 79.7, 42.7, 40.6, 28.6, 26.3. MS (MALDI-TOF) (mass spectroscopy: matrix assisted laser desorption ionization - time of flight) m/z 340 $[M + K]^+$, 324 $[M + Na]^+$. Calculated analysis for $C_{12}H_{19}N_3O_6$: C, 47.84; H, 6.36; N, 13.95. Found: C, 48.09; H, 6.65; N, 14.00.

(S)-*O*-succinimidyl-2-(*tert*-butoxycarbonylamino)propylcarbamate (Ib). Boc-β^3-HAla-OH (3.25 g, 16 mmol) is transformed by following the general procedure.

Recrystallization in toluene gives the compound (Ia) (3.05 g, 60% which is a white solid; mp. 153-155°C; $[\alpha]_D^{r.t.}$ - 14.4 (*c* 1.03, MeCN); HPLC t_R 8.00 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 1.07 (d, J = 6.8 Hz, 3H), 1.41 (s, 9H), 2.73 (s, 4H), 3.14-3.20 (m, 2H), 3.62-3.72 (m, 1H), 5.25 (br d, 1H), .6.54 (br t, 1H). ^{13}C-NMR (50 MHz, CD_3CN): 171.7, 156.7, 153.3, 79.6, 47.7, 47.4, 28.7, 26.3, 18.4. Calculated analysis for $C_{13}H_{21}N_3O_6$: C, 49.52; H, 6.71; N, 13.33. Found: C, 49.45; H, 6.57; N, 13.18.

***(S)-O*-succinimidyl-2-*(tert*-butoxycarbonylamino*)*-(II)-methylbutylcarbamate (Ic).** Boc-β^3-HVal-OH (1.27g, 5.5 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (Ic) (956 mg, 51%) which is a white solid; mp. 125-127°C; $[\alpha]_D^{r.t.}$ - 41.2 (*c* = 1.15,THF, $CHCl_3$); HPLC t_R 10.80 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 0.89 (t, J = 7.0 Hz, 6H), 1.42 (s, 9H), 1.65-1.78 (m, 1H), 2.73 (s, 4H), 3.11-3.52 (m, 3H), 5.18 (br d, J = 8.5 Hz, 1H), 6.46 (br t, 1H). ^{13}C-NMR (50 MHz, CD_3CN): 171.7, 157.7, 153.5, 79.3, 56.7, 44.8, 31.0, 28.7, 26.3, 19.8, 18.3. MS (MALDI-TOF) m/z 383 $[M + K]^+$, 367 $[M + Na]^+$. Calculated analysis for $C_{15}H_{25}N_3O_6$: C, 52.47; H, 7.34; N, 12.24. Found: C, 52.26; H, 7.13; N, 11.92.

***(S)-O*-succinimidyl-2-*(tert*-butoxycarbonylamino*)*-4-phenyl-propylcarbamate (Id).** Boc-β^3-HPhe-OH (8.27g, 29.5 mmol) is transformed by following the general procedure. Recrystallization in toluene gives the compound (Id) (6.6g, 57%) which is a white solid; mp. 163-164°C; $[\alpha]_D^{r.t.}$ -15 (*c* 1.17, MeCN); HPLC t_R 12.79 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 1.33 (s, 9H), 2.68-2.90 (m, 6H), 3.16-3.37 (m, 2H), 3.78-3.93 (m, 1H), 5.26 (d, J = 8.0 Hz, 1H), .6.54 (br t, 1H); 7.16-7.34 (m, 5H). ^{13}C-NMR (50 MHz, CD_3CN): 171.7, 157.3, 153.3, 139.4, 130.3, 129.4, 127.4, 79.6, 53.2, 46.3, 39.0, 28.6, 26.3. MS (MALDI-TOF) m/z 430 $[M + K]^+$, 414 $[M + Na]^+$. Calculated analysis for $C_{19}H_{25}N_3O_6$: C, 58.30; H, 6.44; N, 10.74. Found: C, 58.17; H, 6.38; N, 10.69.

***(S)-O*-succinimidyl-3-(benzyloxycarbonyl)-2-*(tert*-butoxycarbonylamino*)* propyl-carbamate (Ie).** Boc-β^3-HAsp(Bzl)-OH (2.53g, 7.5 mmol) is transformed by

following the general procedure. Recrystallization in toluene gives the compound (Id) (1.94g, 58%) which is a white solid; mp. 115-117°C; $[\alpha]_D^{r.t.}$ - 16.3 (*c* 1.3, THF); HPLC t_R 13.47 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 1.46 (s, 9H), 2.47-2.58 (m, 2H); 2.73 (s, 4H), 3.29 (t, J = 6.2 Hz, 2H), 3.96-4.08 (m, 1H), 5.10 (s, 2H), 5.45 (br d, J = 6.2 Hz, 1H); 6.54 (br t, 1H); 7.29-7.41 (m, 5H). ^{13}C-NMR (50 MHz, CD_3CN): 26.3, 28.7, 37.6, 45.8, 48.9, 67.2, 80.0, 118.3, 129.1, 129.6, 137.3, 153.4, 156.5, 171.6, 171.7. MS (MALDI-TOF) m/z 488 $[M + K]^+$, 472 $[M + Na]^+$. Calculated analysis for $C_{21}H_{27}N_3O_8$: C, 56.12; H, 6.05; N, 9.35. Found: C, 55.89; H, 6.01; N, 9.32.

(*S*)-*O*-succinimidyl-3-(benzyloxy)-2-(*tert*-butoxy-carbonylamino)-propylcarbamate (If). Boc-β^3-HThr(Bzl)-OH (2.31g, 7.14 mmol) is transformed by following the general procedure. Recrystallization in AcOEt/hexane gives the compound (Id) (2.0g, 64%) which is a white solid; mp. 109-110°C; $[\alpha]_D^{r.t.}$ + 8.6 (*c* 1.07, CH_3CN); HPLC t_R 14.59 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 1.16 (d, J = 6.1 Hz, 3H), 1.43 (s, 9H), 2.73 (s, 4H), 3.21-3.44 (m, 2H), 3.61-3.76 (m, 2H), 4.51 (Abq, J = 11.5 Hz, 2H), 5.21 (br d, J = 9.1 Hz, 1H), 6.49 (br t, 1H), 7.25-7.39 (m, 5H). ^{13}C-NMR (50 MHz, CD_3CN): 16.4, 26.3, 28.6, 44.1, 55.3, 71.5, 75.1, 128.5, 128.8, 129.3. MS (MALDI-TOF) m/z 475 $[M + K]^+$, 459 $[M + Na]^+$. Calculated analysis for $C_{21}H_{29}N_3O_7$: C, 57.92; H, 6.71; N, 9.65. Found: C, 58.02; H, 6.67; N, 9.81.

***O*-succinimidyl-(2-nitrophenyl)carbamate (Ig) (see figure 1).** 2-nitrobenzoic acid (1.17g, 7 mmol) is transformed by following the general procedure. Recrystallization in AcOEt gives the compound (Ig) (1.39g, 71%) which is present in the form of light yellow crystals; mp. 166-167°C; HPLC t_R 9.45 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, $CDCl_3$): 2.89 (s, 4H), 7.26 (dt, 1H), 7.69 (dt, 1H), 8.26 (dd, 1H), 8.40 (dd, 1H), 10.40 (br s). ^{13}C-NMR (50 MHz, $CDCl_3$): 25.6, 120.8, 124.1, 126.2, 133.1, 136.2, 148.5, 169.2. MS (MALDI-TOF) m/z 318 $[M + K]^+$, 302 $[M + Na]^+$. Calculated analysis for $C_{12}H_{10}N_2O_6$: C, 47.32; H, 3.25; N, 15.05. Found: C, 47.45; H, 3.26; N, 15.07.

Formation of ureas: general procedure. O-succinimidyl carbamate (I) (1 mmol) and Hunig base (1 mmol) are added to a solution of the amine (1.3 mmol) in 5 ml DMF. After 10-30 minutes, the reaction mixture is diluted with saturated $NaHCO_3$, and extracted with AcOEt. The organic phase is washed with 1 N $KHSO_4$, saturated NaCl, $NaHCO_3$, saturated NaCl, dried ($MgSO_4$) and evaporated. Chromatography and/or recrystallization give the pure urea (VI).

Methyl *(2S, 3R)*-2-{[2-*(tert*-Butoxycarbonylamino)ethyl]-ureido}-3-methyl-pentanoate (Boc-G^{u}CH$_2$-Leu-OMe, (VIa)). The carbamate (Ia) (602 mg, 2 mmol) is treated with HCl·H-Leu-OMe (436 mg, 2.4 mmol) following the general procedure. Recrystallization in EtOAc/diisopropylether gives (VIa) (520 mg, 78%) which is present in the form of colorless needles; mp. 86-89°C; $[\alpha]_D^{r.t.}$ - 10.8 (*c* 1.02, MeOH); HPLC t_R 11.39 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, $CDCl_3$): 0.90 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H), 1.41 (s, 9H), 1.45-1.75 (m, 3H), 3.16-3.32 (m, 4H), 3.69 (s, 3H), 4.36-4.47 (m, 1H), 5.34 (br t, J = 5.2, 1H), 6.14 (d, J = 8.2, 1H), 6.76 (br t, J = 5.0, 1H). ^{13}C-NMR (50 MHz, $CDCl_3$): 21.9, 22.9, 24.8, 28.4, 40.3, 41.3, 41.8, 51.7, 52.1, 79.4, 156.7, 158.5, 175.3. MS (MALDI-TOF) m/z 370 $[M + K]^+$, 354 $[M + Na]^+$, 332 $[M + 1]^+$. Calculated analysis for $C_{15}H_{29}N_3O_5$: H_2O: C, 52.94; H, 8.82; N, 12.35. Found: C, 52.92; H, 8.68; N, 12.27.

***(2S)*-1-[2-*(tert*-Butoxycarbonylamino)-propyl]-3-(1-methyl-ethyl)-urea (Boc-A^{u}CH$_2$-*i*-Pr, (VIb)).** The carbamate (Ib) (901 mg, 2.86 mmol) is treated with i-PrNH_2 (511 l, 6 mmol) according to the general procedure to give (VIb) (701 mg, 95%) which is a white solid; mp. 101°C; $[\alpha]_D^{r.t.}$ - 7.4 (*c* 0.89, MeOH); HPLC t_R 8.71 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3CN): 1.03 (d, J = 6.6 Hz, 3H), 1.07 (d, J = 6.5 Hz, 6H), 1.40 (s, 9H), 3.02-3.08 (m, 2H), .3.47-3.60 (m, 1H), 3.65-3.81 (m, 1H), 4.92 (br d, 1H); 5.1 (br t, 1H), 5.66 (br, 1H); ^{13}C-NMR (50 MHz, CD_3CN): 158.4, 156.4, 79.4, 47.7, 46.2, 42.2, 28.5, 23.4, 23.3, 18.6. MS (MALDI-TOF) m/z 298 $[M + K]^+$, 282 $[M + Na]^+$. Calculated analysis for $C_{12}H_{25}N_3O_3$: C, 55.57; H, 9.72; N, 16.20. Found: C, 55.56; H, 9.82; N, 16.16.

***(2S)*-1-[2-*(tert*-Butoxycarbonylamino)-3-phenyl-propyl]-3-phenyl-urea (Boc-F^{u}CH$_2$-Ph, (VIc)).** The carbamate (Id) (500 mg, 1.28 mmol) is treated with $PhNH_2$ (119 mg, 1.28 mmol) according to the general procedure. A recrystallization in CH_2Cl_2/hexane gives (VIc) (412 mg, 87%) which is a white solid. mp. 154 °C; $[\alpha]_D^{r.t.}$ + 10.3 (*c* 1.03, MeOH); HPLC t_R 15.23 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (400 MHz, CD_3OD): 1.35 (s, 9H), 2.70 (dd, *J* = 8.0, 13.7 Hz, 1H), 2.80 (dd, *J* = 7.8, 13.7 Hz, 1H), 3.16 (dd, *J* = 8.6, 13.6 Hz, 1H), 3.33 (dd, *J* = 4.6, 17.1 Hz, 1H), 3.81-3.85 (m, 1H), 7.16-7.34 (m, 10H). ^{13}C-NMR (400 MHz, CD_3OD): 158.8, 158.6, 141.3, 140.1, 130.8, 130.2, 129.8, 127.7, 123.9, 120.7, 80.4, 54.6, 44.8, 40.3, 29.1, 28.8. MS (MALDI-TOF) m/z 408 $[M + K]^+$, 392 $[M + Na]^+$, 370 $[M + 1]^+$. Calculated analysis for $C_{21}H_{27}N_3O_3$: C, 68.27 ; H, 7.37 ; N, 11.37. Found: C, 68.19 ; H, 7.32 ; N, 11.47.

Boc-F^{u}CH$_2$-Pro-NH$_2$, (VId). The carbamate (Id) (1.16g, 3 mmol) is treated with HCl·H-Pro-NH_2 (540 mg, 3.6 mmol) according to the general procedure. A chromatography ($CHCl_3$/MeOH 10:1) gives (VId) (1.16g, 88%) which is a white solid; mp. 96-98 °C; $[\alpha]_D^{r.t.}$ – 20.4 (*c* 1.02, MeOH); HPLC t_R 10.02 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3OD): 1.36 (s, 9H), 1.88-2.17 (m, 4H), 2.59-2.83 (m, 2H), 2.96 (dd, *J* = 9.4, 13.6 Hz, 1H), 3.21-3.50 (m, 3H), 3.89-3.99 (m, 1H), 4.29 (dd, *J* = 3.2, 8.1 Hz, 1H), 7.11-7.29 (m, 5H). ^{13}C-NMR (200 MHz, $CDCl_3$): 24.7, 28.4, 28.8, 39.0, 45.7, 46.3, 51.6, 60.1, 79.6, 126.6, 128.6, 129.2, 137.4, 156.6, 157.8, 175.4. MS (MALDI-TOF) m/z 429 $[M + K]^+$, 413 $[M + Na]^+$, 391 $[M + 1]^+$. Calculated analysis for $C_{20}H_{30}N_4O_4$: C, 61.52; H, 7.74. Found: C, 61.78 H, 7.77.

Boc-A^{u}CH$_2$-A^{u}CH$_2$-*i*-Pr, (VIe). The product (VIb) (650 mg, 2.5 mmol) is dissolved in CF_3COOH (0.25M) at 0°. After agitation at ambient temperature for 30 minutes and concentration under reduced pressure, the trifluoroacetate salt is dried under vacuum under KOH and used without further purification.

The carbamate (Ib) is treated with a solution of trifluoroacetate salt according to the general procedure. Recrystallization in EtOH/hexane gives (VIe) (630 mg, 70%) which is a white solid. mp. 184-185°C, $[\alpha]_D^{r.t.}$ + 9.3 (*c* 0.88, MeOH); HPLC t_R 8.52 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3OD): 1.05-1.12 (m,

12H), 1.42 (s, 9H), 2.92-3.24 (m, 4H), 3.56-3.84 (m, 2H); ^{13}C-NMR (100 MHz, CD_3OD): 160.9, 160.7, 158.2, 80.0, 48.2, 47.8, 46.8, 46.4, 42.9, 28.5, 23.6, 23.5, 19.1, 18.6. Calculated analysis for $C_{16}H_{33}N_5O_4$: C, 53.46; H, 9.25; N, 19.48. Found: C, 53.62; H, 9.29; N, 19.43.

Boc-A^{u}CH$_2$-A^{u}CH$_2$-A^{u}CH$_2$-*i*-Pr, (VIf). The product (VIe) (440 mg, 1.22 mmol) is dissolved in CF_3COOH (0.25M) at 0°. After agitation at ambient temperature and concentration under reduced pressure the trifluoroacetate salt, which precipitates by addition of Et_2O, is collected by filtration, dried under vacuum under KOH and is used without further purification.

To a solution of this salt in DMF are added successively (Ib) and Hunig base (637 l, 3.66 mmol). The reaction mixture is agitated for 20 minutes and saturated $NaHCO_3$ is added. The precipitate which forms is filtered, washed with saturated $NaHCO_3$, water, and Et_2O and is dried under vacuum on P_2O_5 to give (VIf) (350 mg, 62%) which is a white solid. mp. 210-211°C, $[\alpha]_D^{r.t.}$ 63.6 (*c* 1.00, MeOH); HPLC t_R 8.53 min (linear gradient, 20-80% B, 20 min); ^{1}H-NMR (200 MHz, CD_3OD): 1.03-1.12 (m, 15H), 1.44 (s, 9H), 2.55-2.85 (m, 3H), 3.21-3.39 (m, 3H), 3.61-3.95 (m, 4H); ^{13}C-NMR (100 MHz, CD_3OD): 161.2, 161.1, 160.9, 158.7, 80.3, 48.2, 47.6, 47.5, 47.2, 47.1, 46.8, 43.0, 29.0, 23.8, 23.7, 19.5, 19.0, 18.7. MS (MALDI-TOF) m/z 499 $[M + K]^+$, 483 $[M + Na]^+$, 461 $[M + 1]^+$. Calculated analysis for $C_{20}H_{41}N_7O_5$: C, 52.27; H, 8.99; N, 21.33. Found: C, 52.23; H, 9.00; N, 20.93.

Example II:

Preparation of *O*-succinimidyl-2-[(*9H*-fluoren-9-yl-methoxy)carbonylamino]-ethylcarbamate derivatives from *β*-amino acids and application to the synthesis in solid phase of oligoureas and of pseudopeptide urea:

1/ Preparation of O-succinimidyl carbamates.

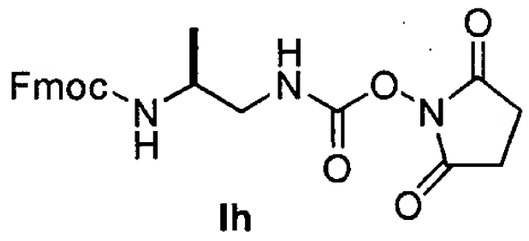
An efficacious synthesis of *O*-succinimidyl-2-[(*9H*-fluoren-9-ylmethoxy)carbonylamino]ethylcarbamate derivatives is described as well as their use as activated monomers in the synthesis of di- and tri-substituted ureas and urea

oligomers. The *N*-Fmoc-protected *β*-aminoacids are first transformed into the corresponding acyl azide derivatives. The isocyanate formed by Curtius rearrangement of these compounds is immediately treated with N-hydroxysuccinimide in the presence of pyridine to give the corresponding carbamates Ih and Ii (61-86%).

Procedure for obtaining O-succinimidyl carbamates. The *N*-protected *β*-amino acid (10 mmol) is dissolved in THF (30 ml) under Ar and cooled to -20°. After addition of *i*-BuOCOCl (11 mmol) and NMM (11 mmol, 1.1. equivalent), the reaction mixture is agitated at -20° for 20 minutes. The resulting white suspension is reheated to -5°, and is treated with a solution (5 ml) of NaN_3 (25 mmol). The mixture is then agitated for 5 minutes, diluted with EtOAc, washed with saturated NaCl, dried on $MgSO_4$ and concentrated under reduced pressure to give the acyl azide which is used without further purification. Toluene is then added under argon and the resulting solution is heated to 65°C with agitation. Once the emission of gas has ceased (about 10 minutes), the N-hydroxysuccinimide (10 mmol) and the pyridine (10 mmol) are added. The mixture is agitated for 5 minutes at 65°C and cooled to ambient temperature. In most cases, the desired product crystallizes in the toluene solution and is collected by filtration. Recrystallization in toluene permits obtaining pure O-succinimidyl carbamate. Otherwise, the solvent is evaporated under vacuum and the residue is purified by recrystallization in the appropriate solvant.

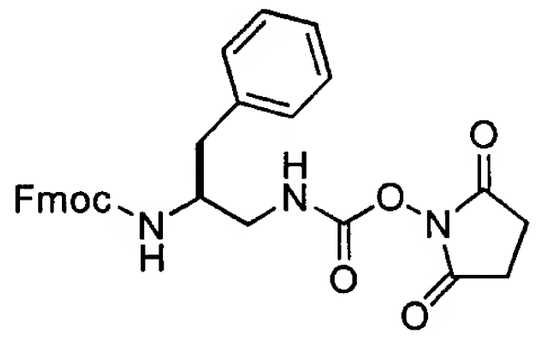
***(S)-O*-succinimidyl-2-[*(9H*-fluoren-9-ylmethoxy)carbonylamino]propyl carbamate (Ih).**

Fmoc-β^3-HAla-OH (3.39 g, 10.46 mmol) is transformed according to the procedure. A recrystallisation in toluene gives the expected carbamate (4.41 g, 86%) in the form of a white solid.



Ih

***(S)-O*-succinimidyl-2-[*(9H*-fluoren-9-ylmethoxy*)*carbonylamino]-4-phenyl-propylcarbamate (Ii).** Fmoc-β^3-HPhe-OH (4.73g, 11.8 mmol) is transformed according to the general procedure. A recrystallisation in toluene gives 4d (3.64g, 61%) in the form of a white solid.



Ii

2/ Application to synthesis on a solid support.

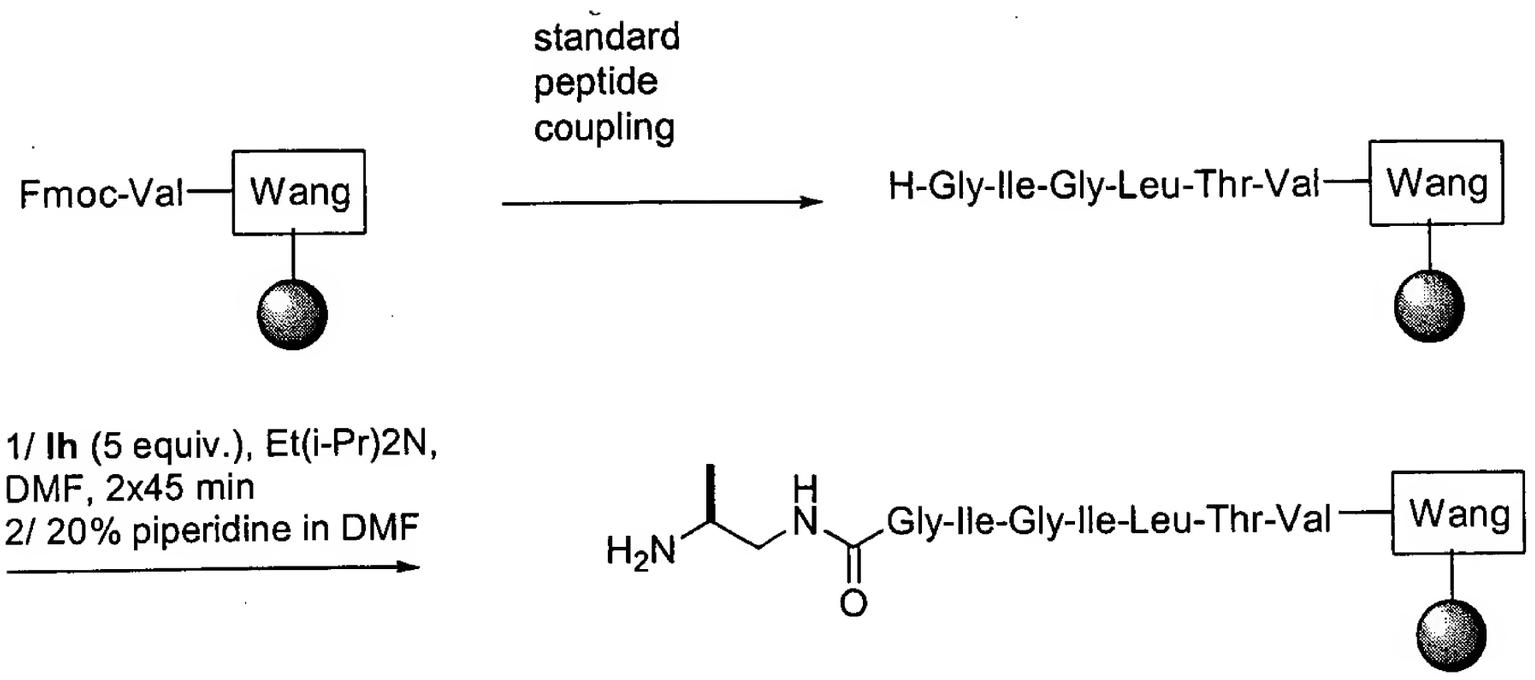
Incorporation of a urea structure in a peptide.

The peptide sequence selected by way of example is that of the tumoral antigen MART(27-35) of the sequence:

H-Ala-Ala-Gly-Ile-Gly-Ile-Leu-Thr-Val-OH.

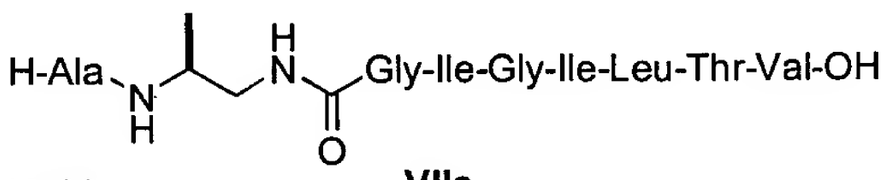
The use of the carbamate (Ih) has permitted the introduction of a urea structure between Ala^{28} and Gly^{29}.

The synthesis in solid phase of the peptide up to Gly^{29} is carried out by Fmoc chemistry (Fluorenyl methoxycarbonyl) on a scale of 100 moles by starting with a Wang resin (p-benzyloxybenzyl alcohol) substituted with valine according to conventional methods of synthesis of peptides in solid phase (References: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed: G.B. Fields, Academic Press, NY, USA). After deprotection of the Fmoc group of Gly^{29} with 20% piperidine in DMF, the carbamate (Ih) (5 equivalents) dissolved in DMF followed by diisopropylethylamine (5 equivalents) are added to the resin, and the reaction is left to proceed for 45 minutes. This operation can if desired be repeated once. After washing and rinsing of the resin, the Fmoc group is deprotected as above, and Fmoc-Ala-OH is coupled to the resin by using methods described in the literature (references: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed: G.B. Fields, Academic Press, NY, USA).



VIIa

After cleaving the resin by conventional protocols used in peptide synthesis in solid phase (references: Methods in Enzymology, Vol. 89, Solid Phase Peptide Synthesis, Ed.: G.B. Fields, Academic Press, NY, USA), the desired crude product (VIIa) is obtained after lyophilization with a purity of 73% (by HPLC). After purification by HPLC and lyophilization, the product is obtained with a purity of 99.2%. The pure product is characterized by mass spectrometry (MALDI-MS) and by HPLC.



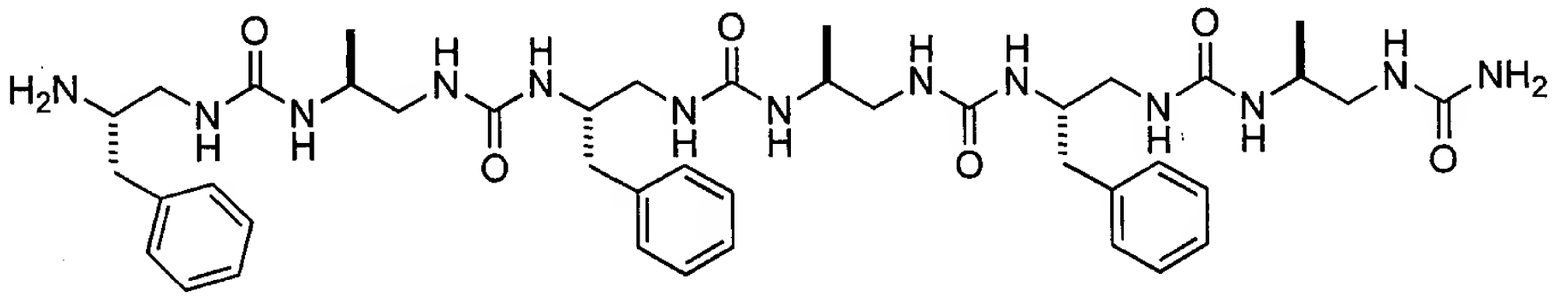
VIIa

-MALDI-MS: 843.93

-HPLC retention time: 12.34 min: (A: 0.08% TFA in H_2O; B: 0.08% TFA in CH_3CN, 5-65% B in 20 minutes) (TFA= trifluoroacetic acid).

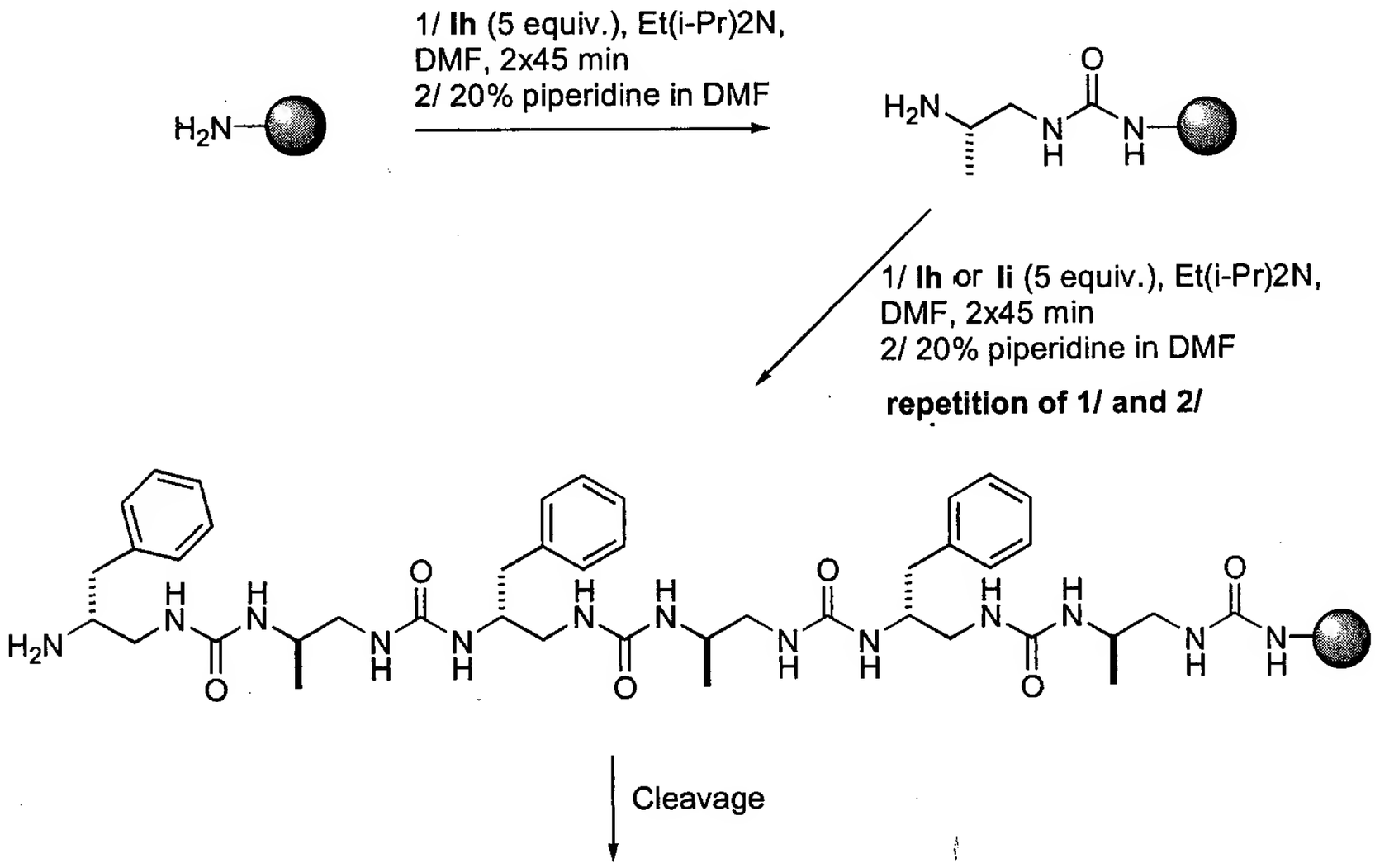
Synthesis of an urea oligomer from carbamates (Ih) and (Ii).

The product (VIIb) has been synthesized in solid phase from a commercial Rink amide resin (4-(2',4'-dimethoxyphenyl-Fmoc-aminomethyl)phenoxyacetamido-4-methylbenzhydrylamine resin) on a scale of 100 µmole.



VIIb

The carbamate (Ih) (5 equiv.) in 2ml of DMF is added to a suspension of the resin in DMF (2ml) followed by diisopropylethylamine (5 equiv.). The reaction is left to run 45 minutes and repeated, after filtration of the resin. The Fmoc group is then cleaved by treated with 20% piperidine in DMF. The washing and filtration techniques of the resin as well as the deprotection of the Fmoc group are those currently used in peptide synthesis in solid phase. The whole operation (coupling and deprotection of the Fmoc) is repeated several times with carbamates (Ii) and (Ih) alternating, to give, after cleavage of the resin (standard cleavage used in peptide synthesis in solid phase with the Fmoc strategy) the crude product (VIIb) with a 63% purity (determined by HPLC). The pure product is characterised by mass spectroscopy (MALDI-MS) and by HPLC.



VIIb

-MALDI-MS: 847.25

-HPLC retention time: 10.87 min: (A: 0.08% TFA in H_2O; B: 0.08% TFA in CH_3CN, 5-65% B in 20 minutes) (TFA= trifluoroacetic acid).

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(8) It is interesting to note that in the synthesis of oligoanthranilamides, the Hamilton group uses 2-nitrobenzoic acid in place of N-benzoylanthranilic acid. In this case, the nitro group as the masking group of the amine is necessary to avoid the formation of azlactone: Hamuro, Y.; Geib, S.J.; Hamilton, A.D. *J. Am. Chem. Soc.* **1996** 118, 7529.

(9) We have used the code with a letter proposed by Burgess for the urea oligomers[3b]. As an alternative, we propose the following abbreviation which permits the use of the code with a letter for the amino acids: Boc(-β^3-HAla^u)$_2$-*i*-Pr (VIe) and Boc(-β^3-HAla^u)$_3$-*i*-Pr (VIf). According to the nomenclature of Spatola[11] for the pseudopeptides, we can also write: Boc(-β^3-HAla-[NHCONH])$_2$-*i*-Pr (VIe) et Boc(-β^3-HAla-[NHCONH])$_3$-*i*-Pr (VIf).

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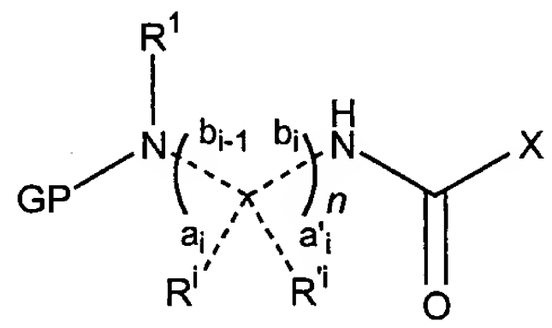
CLAIMS

1. Use of isocyanates obtained from amino acid derivatives for the preparation and if desired the isolation of stable activated carbamates.

2. Use of isocyanates or of stable activated carbamates according to claim 1, for the preparation of substituted ureas, cyclic or not, particularly of oligomers of ureas, cyclic or not, or for the preparation of peptides or pseudo-peptides containing urea designs, cyclic or not.

3. Compounds of formula (I):



(I)

in which

– "n" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form parts of aromatic rings,

– GP is a protective group selected from:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),

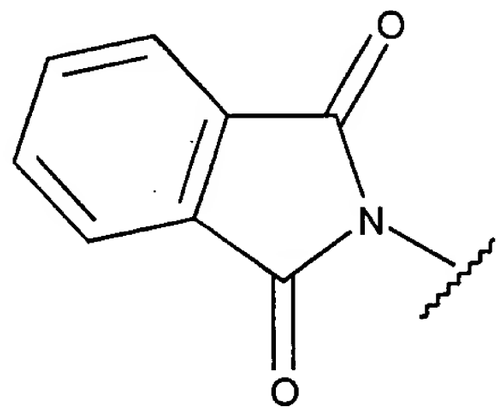
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide ($R^1 = Ø$)



* O_2 (corresponds to a nitro group as masked form of the amine), $R^1 = Ø$

– the groups R_1, R_i, R'_i and R can each represent independently one of the other:

hydrogen,

halogen,

the side chain of amino acid selected from natural or synthetic amino acids,

an alkyl (C1-C20) group, substituted or not with one or several of the following substituents:

1/ $-COOR_a$

2/ $-CONHR_a$

3/ -COOH

4/ -OH

5/ $-OR_a$

6/ -NHR

7/ $-NH_2$

8/ $-NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an alcoxy group OR_a

a NH_2 group

an OH group

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the group X represents a group conferring on the compound of formula I an activated carbamate structure, selected particularly from phenols, if desired substituted with at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

– N-hydroxysuccinimide

– phenol

– pentafluorophenol

– pentachlorophenol

– p-nitrophenol

– 2,4-dinitrophenol

– 2,4,5-trichlorophenol

– 2,4-dichloro-6-nitrophenol

– hydroxy-1,2,3-benzotriazole

– 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)

– 7-aza-1-hydroxybenzotriazole (HOAt)

– 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compound of formula (I) having the following property:

– if one or several asymmetric carbons are present in the formula (I), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R_1, R_i, R'_i can also be defined on the basis of intramolecular cyclizations which are as follows:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i or R'^i and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i or R'^i wherein preferably i = 1, 2, 3 or 4,

provided that the compound of formula (I) is different from the following compounds, in which:

– n=2, GP=Boc, R_1 = isobutyl, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol,

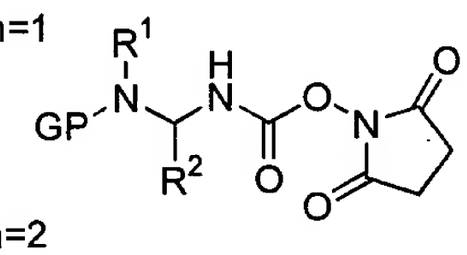
– n=2, GP=Boc, R_1 = benzyl, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol,

– n=2, GP=Boc, R_1 = CH_2-p-C_6H_4O*t*-Bu, $R_2=R'_2=R_3=R'_3$=H, X = 4-nitrophenol,

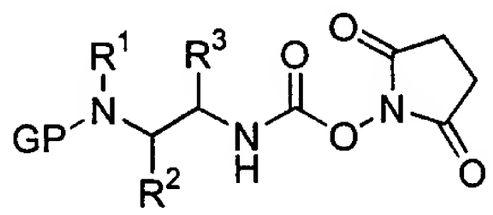
– n=2, GP=Boc, R_1 = H, $R_2 = R'_2 = R_3 = R'_3$ = H, X = 4-nitrophenol.

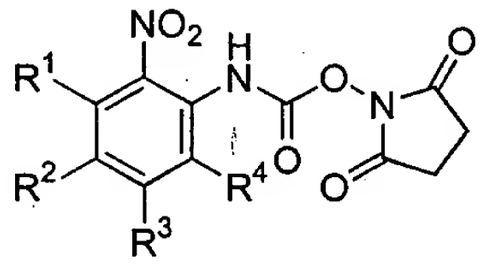
4. Compounds according to claim 3, of formula (I) in which $1 \geq n \geq 4$, X = N-hydroxysuccinimide and GP is an urethane or acyl group such as defined in claim 3, and particularly the following compounds, in which GP is advantageously Boc, Fmoc or O_2,

n=1

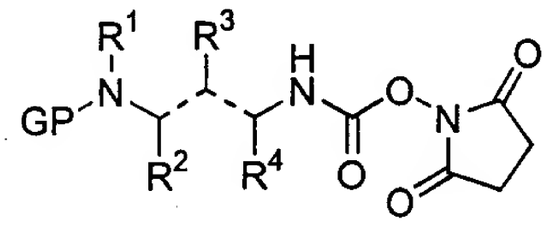


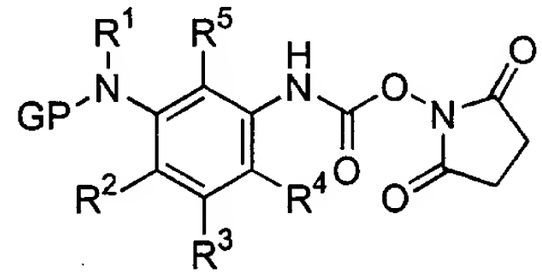
n=2



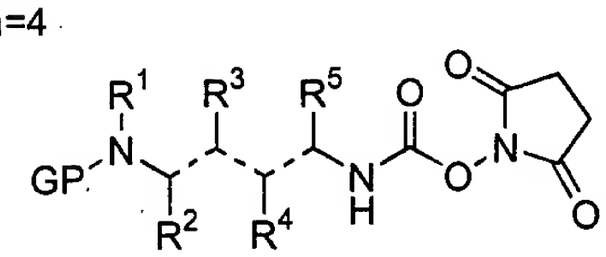


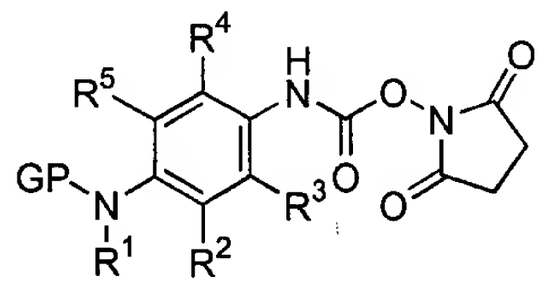
n=3





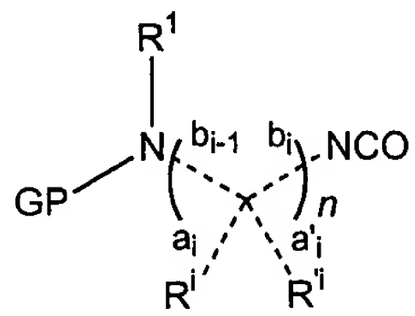
n=4





the binding with a broken line, representing a simple or double binding, with the proviso that a double binding is not contiguous to another double binding.

5. Compounds of formula (II):



(II)

in which

– "n" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "i" is a number varying from 2 to n+1,

– a_i and a'_i, represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s)
* if b_i = d then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d then b_{i-1} and b_i = s

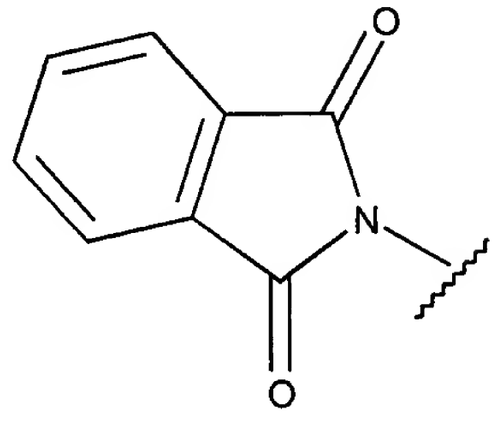
certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– GP is a protective group chosen among:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$)
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = H, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

*phtalimide (R1 = Ø)



* O_2 (corresponds to a nitro group as a masked form of the amine), R^1 = Ø

– the groups R_1, R_i, R'_i and R can each represent independently one of the other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents chosen among:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/-NHR_a

7/-NH_2

8/-$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a alcoxy group

a NH_2 group

an OH group,

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

the compound of formula (I) having the following property:

– if one or several asymmetric carbons are present in the formula (I), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R''^i can also be defined on the basis of intramolecular cyclizations which are the following:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a whole positive number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

– provided that the compound of formula (II) is different from the compounds in which:

– n = 1, GP = Boc or benzyloxycarbonyl, $R_1 = Ø$

– n = 2, GP = phtalimide, $R_1 = Ø$, R_3 = benzyl, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, R_3 = methyl, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = H$, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2$*i*-Pr, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2COO$*t*-Bu, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2\ CH_2\ CH_2\ CH_2NHBoc$, $R'_2 = R_2 = R'_3 = H$

– n = 2, GP = phtalimide, $R_1 = Ø$, $R_3 = CH_2\ CH_2\ CH_2NHCNH$(N-Mtr), $R'_2 = R_2 = R'_3 = H$, (Mtr = 4-methoxy-2,3,6-trimethylbenzenesulphonyl)

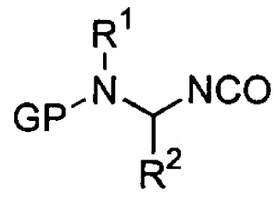
– n = 2, GP = Boc, R_1 = benzyl, $R_2 = R'_2 = R_3 = R'_3 = H$

– n = 2, GP = Boc, R_1 = *i*-Bu, $R_2 = R'_2 = R_3 = R'_3 = H$

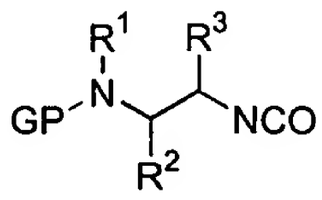
– n = 2, GP = Boc, R_1 = H, R_2 = R'_2 = R_3 = R'_3 = H

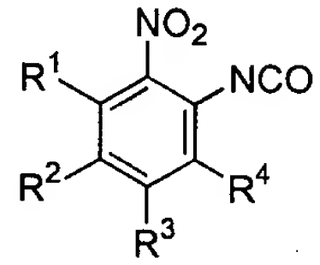
6. Compounds of formula (II) in which $1 \leq n \leq 4$ and GP is an urethane or acyl group as defined in claim 5, and particularly the following compounds, particularly those for which GP= Boc and Fmoc,

n=1

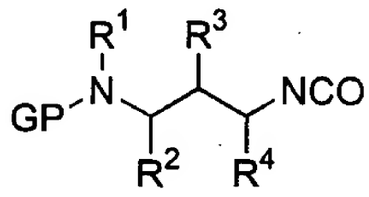


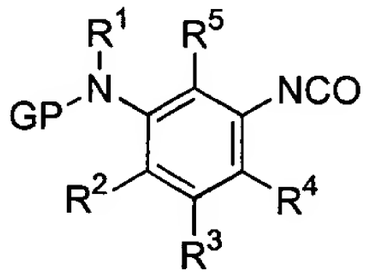
n=2



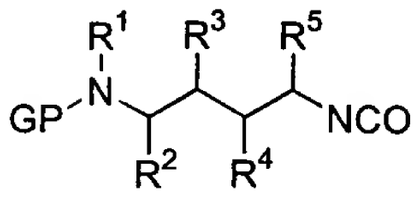


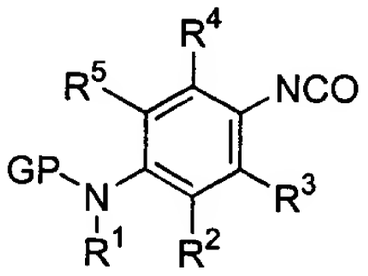
n=3





n=4





7. Compounds according to any of claims 3 to 6, in which the aryl group is chosen among:

1/ phenyl

2/ naphtyl

3/ indenyl

4/ thiophenyl

5/ benzothiophenyl

6/ furanyl

7/ benzofuranyl

8/ pyridyl

9/ indolyl

10/ pyrollyl

or the aryl group non-substituted or substituted with 1 to 6 substituents chosen particularly among:

1/ alkyl of 1 to 10 carbon atoms

2/ halogen

3/ alcoxy of 1 to 10 carbon atoms

4/ hydroxyl

5/ amine of 1 to 10 carbon atoms

6/ ester of 1 to 10 carbon atoms

7/ nitrile

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ nitro

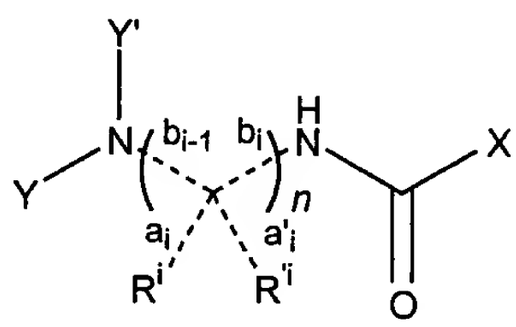
10/ urea of 1 to 10 carbon atoms

11/ amide of 1 to 10 carbon atoms

12/ guanidine

13/ carboxylic acid of 1 to 10 carbon atoms.

8. Compounds of formula (III):



(III)

in which

– "n" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– a_i and a'_i, represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s,
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– the groups R_1, R_i and R'_i can each represent independently one of the other:

hydrogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

-$COOR_a$

-$CONHR_a$

-$CONH_2$

-CH_2COOR_a

-CH_2CONHR_a

-CH_2CONH_2

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the groups Y and Y' can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide bonds)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\Psi_1[*]\text{-}\ldots\text{-}\Psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\Psi_k[*]\text{-}\ldots\Psi_{p-1}[*]C(Z'_p)(Z''_p)\text{-}\Psi_p[*]\text{-}$

– p is a whole number greater than or equal to 1, preferably from 1 to 50, and particularly from 1 to 10,

– k is a whole number varying from 1 to p,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),

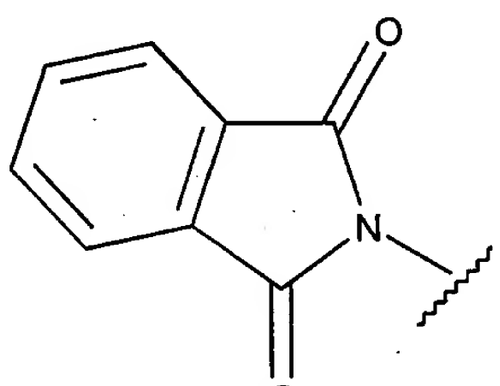
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R1=Ø)



* biotin

– Z_k, Z'_k and Z''_k can each represent independently one of the other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids

a (C1-C20) alkyl group unsubstituted or substituted by one or several constituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -ψ_k[*]- are independently either peptidic linkages CO-NH or bonds of different chemical nature selected particularly from the following list, which is not limiting:

ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO- ; -NHCONH- ; -$COCH_2$ - ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)CONH$- ; -$CH(F_k)CH(F_k')CONH$-

F_k and F_k' representing, independently from each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

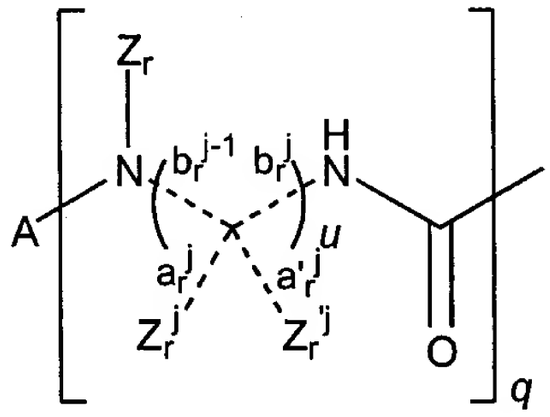
$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}CO\text{-}N(Z_2)\text{-}\ldots\text{-}CO\text{-}N(Z_k)\text{-}C(Z'_k)(Z''_k)\text{-}CO\text{-}N(Z_{k+1})\text{-}\ldots CO\text{-}N(Z_m)\text{-}C(Z'_m)(Z''_m)\text{-}CO\text{-}$

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above

3/ an oligomer of urea having the following formula:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and particularly from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and particularly from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined in the following manner: j always takes the whole values comprised from 2 to u+1,

– or "r" is a whole parameter greater than or equal to 1, always taking values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s,
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s,
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A defined as above

– Z_r, Z_r^j, Z'^j_r are defined independently as above for R^1, R^i, R'^i,

– the X group represents a group giving to the compound of formula I an activated carbamate structure, selected particularly from phenols, if desired substituted by at least one nitro or at least one halogen, or hydroxylamine derivatives, and more particularly selected from the following compounds:

– N-hydroxysuccinimide
– phenol
– pentafluorophenol
– pentachlorophenol
– p-nitrophenol
– 2,4-dinitrophenol
– 2,4,5-trichlorophenol
– 2,4-dichloro-6-nitrophenol
– hydroxy-1,2,3-benzotriazole
– 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
– 7-aza-1-hydroxybenzotriazole (HOAt)
– 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compound of formula (III) having the following property:

– if one or several asymmetric carbons are present in the formula (III), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

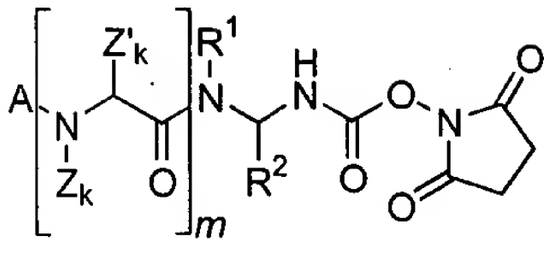
1/ cyclization between R^i and R'^i

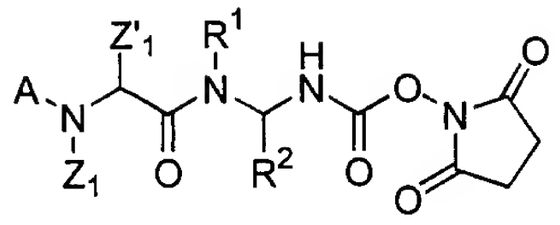
2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a whole positive number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4.

9. Compounds according to claim 8, of formula (III) in which $1 \leq 4 \leq$, X = N-hydroxysuccinimide and GP is an urethane or acyl group and particularly the following compounds in which q and m are comprised from 1 to 10, and preferably equal to 1 or 2, and more particularly those in which GP = Boc and Fmoc or O_2,

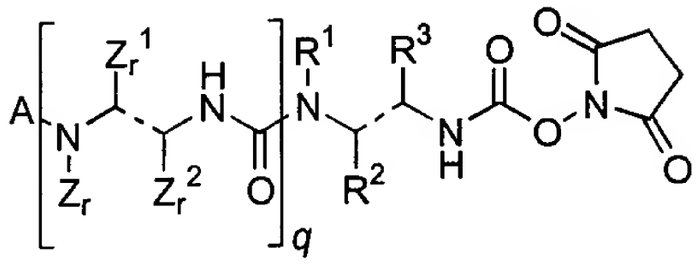
n=1

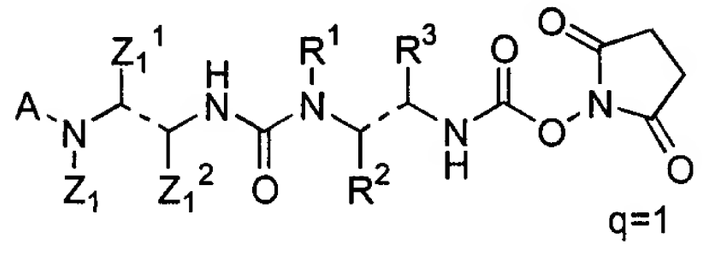




m=1

5 n=2

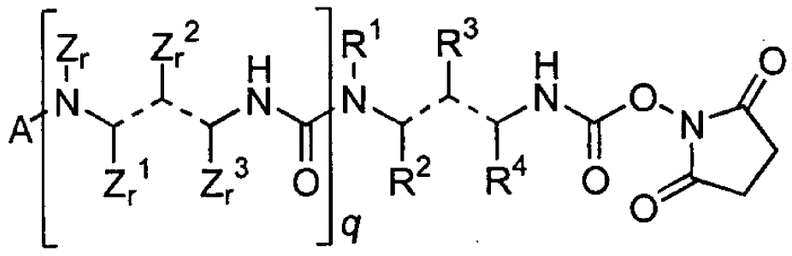


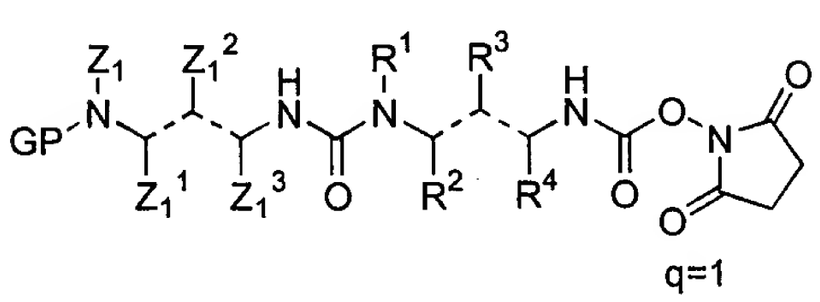


q=1

n=3

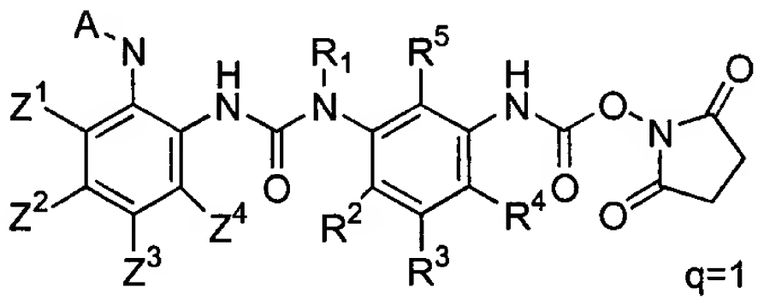
10





q=1

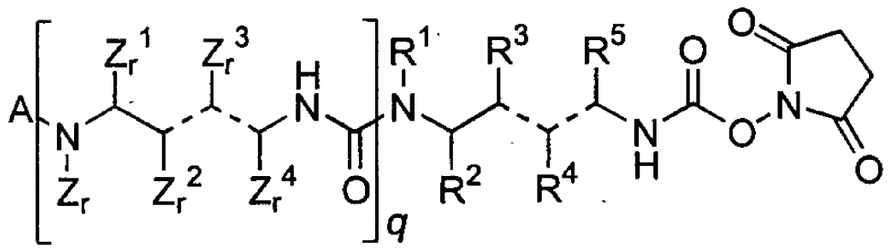
15

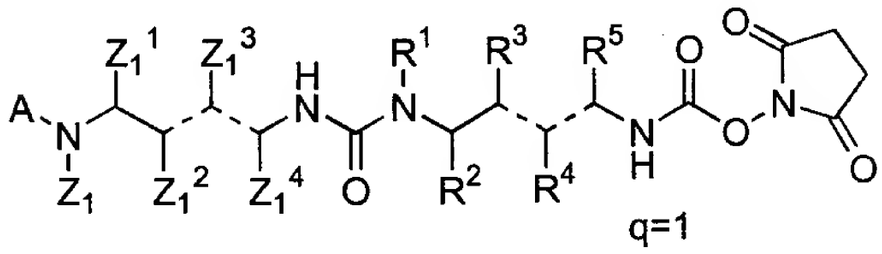


q=1

n=4

20



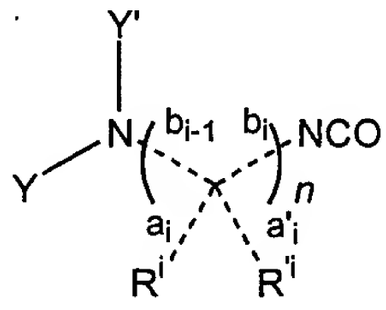


q=1

the broken lines corresponding to single or double bonds, provided that two

25 double bonds are not contiguous.

10. Compounds of formula (IV):



(IV)

30

in which

– "n" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "i" is a whole number varying from 2 to n+1,

– a_i and a'_i represented by a broken line are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}" represented by a broken line are covalent bonds which can be single (s), double (d) or triple (t) with the proviso that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d then b_{i-1} and b_i = s,

certain of these bonds a_i, a'_i, b_{i-1} can also form part of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen

halogen

the side chain of an amino acid selected from natural or synthetic amino acids

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents selected from:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\Psi_1[*]\text{-}\ldots\text{-}\Psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\Psi_k[*]\text{-}\ldots\Psi_{p-1}[*]C(Z'_p)(Z''_p)\text{-}\Psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to p,

– or A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH{=}CH_2$),

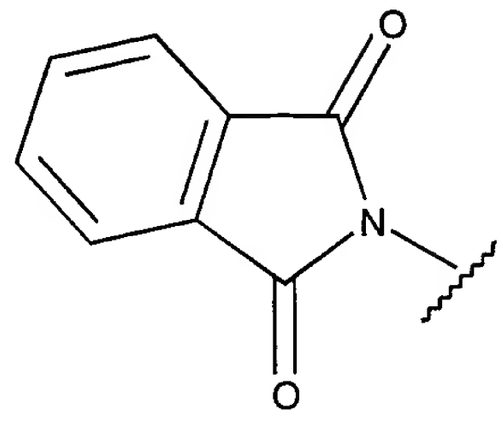
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* phenyl, particularly aryl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R1=Ø)



* biotin

– Z_k, Z'_k and Z''_k can each represent or independently:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, substituted or unsubstituted with one or several substituents from the following:

1/ $-COOR_b$

2/ $-CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ $-NHR_b$

6/ $-NH_2$

7/ $-NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 halogen atoms

$-OR_b$

$-COOR_b$

$-CONHR_b$

$-CONH_2$

$-CH_2COOR_b$

$-CH_2CONHR_b$

$-CH_2CONH_2$

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– $-\Psi_k[*]-$ are independently either peptide linkages CO-NH, or linkages of different chemical nature selected particularly from the following list:

$\psi_k[*]-$ = $-CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; $-NHCO-$; $-NHCONH-$; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF_k'-$; $-CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently from each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

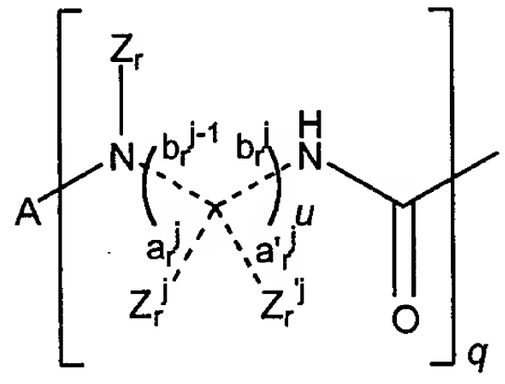
$A-N(Z_1)-C(Z'_1)(Z''_1)-CO-N(Z_2)-\ldots-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-\ldots CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-$

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above,

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2, defined as follows: "j" takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are independently defined as previously for R^1, R^i, R'^i.

the compound of formula (IV) having the following property:

– if one or several asymmetric carbons are present in the formula (IV), then their configuration can be independently either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations which are the following:

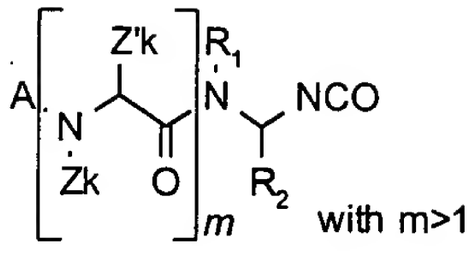
1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (where kc is a positive integer, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4.

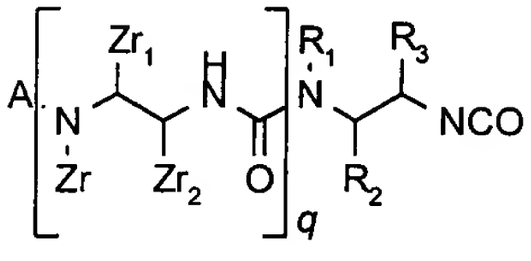
11. Compounds according to claim 10, of formula (IV) in which $1 \leq n \leq 4$ and A is an urethane or acyl group as defined in claim 8, and particularly the following compounds for which q and m are comprised from 1 to 10 and preferably equal to 1 or 2, and particularly those for which A = Boc and Fmoc, and O_2,

n=1

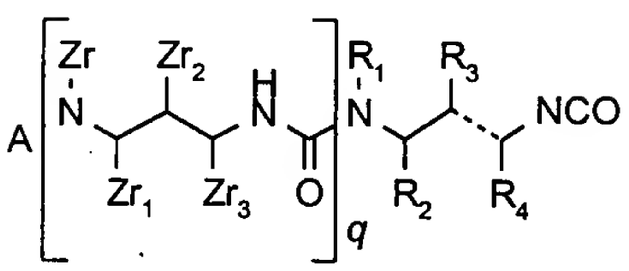


with m>1

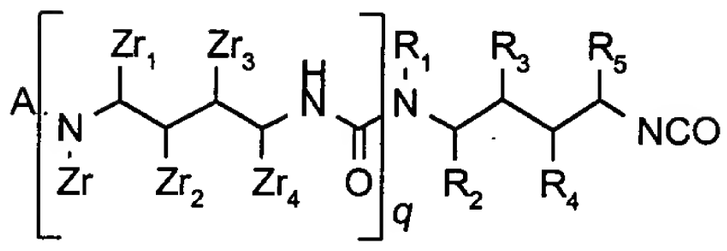
n=2



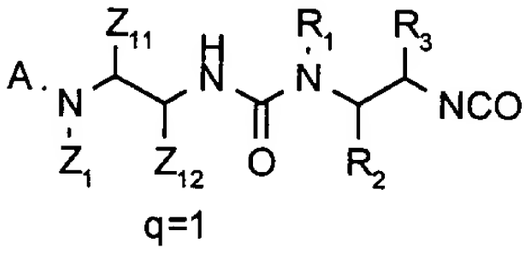
n=3



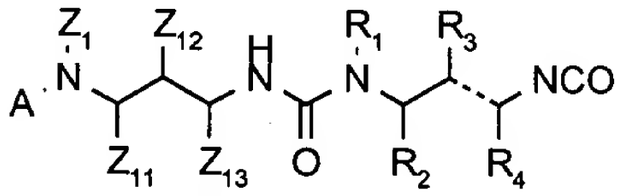
n=4



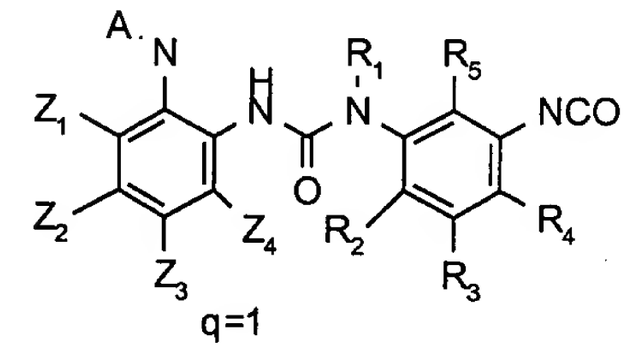
m=1 with A different from Boc (tertbutoxycarbonyl) and from benzyloxycarbonyl



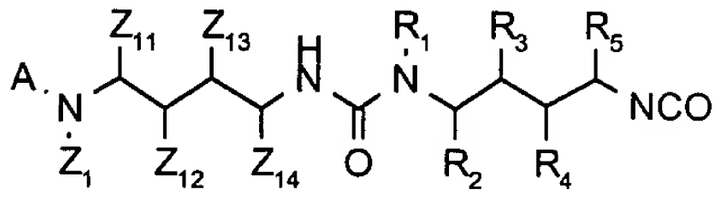
q=1



q=1

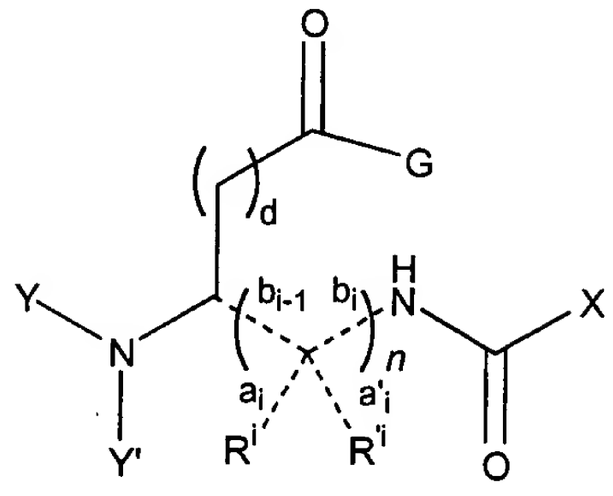


q=1



q=1

12. Compounds of the formula (V)



(V)

in which

– "n" is a whole number greater than or equal to 1, particularly from 1 to 4 and preferably from 1 to 2,

– "d" is a whole number comprised from 0 to 4, preferably equaling 0 or 1,

– "i" is a number varying from 2 to n+1,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds can also form a part of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\psi_1[*]\text{-}\ldots\text{-}\psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\psi_k[*]\text{-}\ldots\psi_{p-1}[*]\text{-}C(Z'_p)(Z''_p)\text{-}\psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH{=}CH_2$),

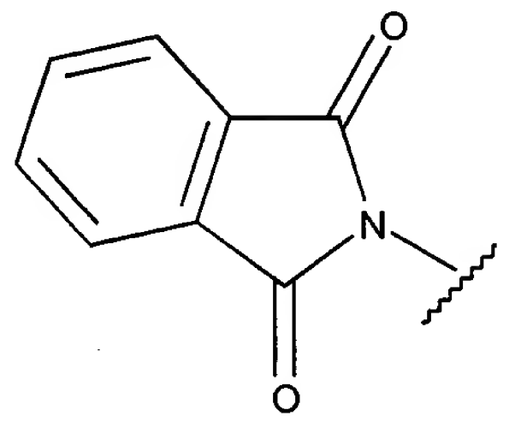
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R^1=Ø)



* biotin

- Z_k, Z'_k, and Z''_k can each represent and independently of one another:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group having 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; -CH_2-CONH- ; $CH(F_k)CONH$- ; -$CH(F_k)CH(F_k')CONH$-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

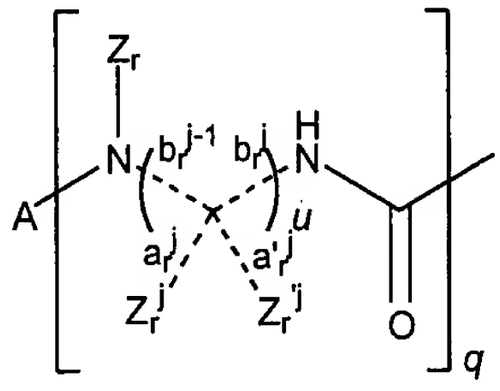
A-$N(Z_1)$-$C(Z'_1)(Z''_1)$-CO-$N(Z_2)$-…-CO-$N(Z_k)$-$C(Z'_k)(Z''_k)$-CO-$N(Z_{k+1})$-…CO-$N(Z_m)$-$C(Z'_m)(Z''_m)$-CO-

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above,

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equel to 2, defined as follows: "j" takes all the whole values comprised from 2 to u+1,

– or "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are independently defined as previously for R^1, R^i, R'^i and R.

– the G group can be or contain:

A/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$$-N(S_1)C(S'_1)(S''_1)-\Psi_1[*]-\ldots-\Psi_{k-1}[*]-C(S'_k)(S''_k)-\Psi_k[*]-\ldots\Psi_{h-1}[*]C(S'_h)(S''_h)-D$$

– "k" is a whole number varying from 1 to h,

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– D can be:

hydrogen,

-COOH

$-COOR_c$

$-CONH_2$

$-CH_2COOR_c$

$-NHCOR_c$

$-CONR_cR_d$'

$-N(R_c)CON(R_d)$

-OH

$-OR_c$

-CN

$-C(O)R_c$

R_c et R_d representing independently of each other an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– or S_k, S'_k and S''_k can each represent independently:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ -COOH

4/ -OH, OR_e

5/ $-NHR_e$

6/ $-NH_2$

7/ $-NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

a halogen

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– $-\Psi_k[*]-$ are independently either CO-NH peptide linkages or linkages of different chemical nature selected particularly from the following list:

$-\Psi_k[*]-$ = $-CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; $-NHCO-$; $-NHCONH-$; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF'_k-$; $CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

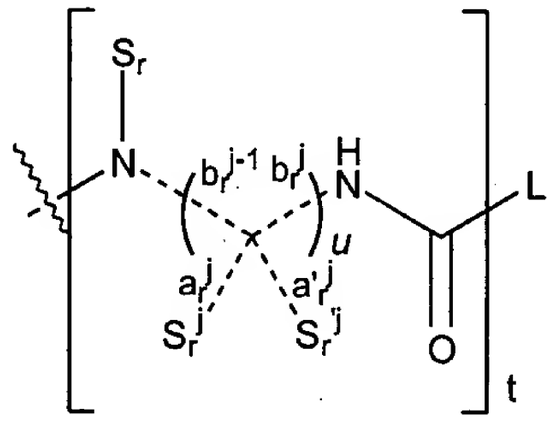
B/ an amino acid residue or an amino acid residue chain:

$-N(S_1)C(S'_1)(S''_1)-CO-N(S_2)-\ldots-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-\ldots CO-N(S_v)-C(S'_v)(S''_v)-D$

– "v" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10, with preferably v>3 and v>5,

– D, S_k, S'_k, and S''_k are independently defined as indicated above,

C/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and a'_r^j", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; a'_r^j and a'_r^{j+1} = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; a'_r^j and a'_r^{j+1} = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds a_r^j, a'_r^j, b_r^j and b_r^{j-1} can also form a part of aromatic rings,

– the group L can be:

$-NH_2$

$-NHR_f$

$-NR_fR_g$

R_f and R_g representing, independently of each other, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_r, S_r^j, S'_r^j, can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and in the case of the proline the groups S_r and S'_r^j or S_r and S_r^j are linked together in order to give the proline cycle,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ -COOH

4/ -OH

5/ -OR_e

6/ NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

-$COOR_e$

-$CONHR_e$

-$CONH_2$

-CH_2COOR_e

-CH_2CONHR_e

-CH_2CONH_2

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the X group represents a group giving to the compound of formula (V) an activated molecule structure adapted to react with alcohols or amines to form carbamates or ureas, and is particularly selected from phenols, if desired substituted with nitro or a halogen, or hydroxylamine derivatives and more particularly selected from:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol

- 2,4-dinitrophenol
- 2,4,5-trichlorophenol
- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

the compounds of formula (V) having the following property:

- if one or several asymmetric carbons are present in formula (V), then their configuration can be in independent manner either R (rectus) or S (sinister),
- the groups R^1, R^i, R'^i groups can also be defined on the basis of intramolecular cyclizations which are the following:

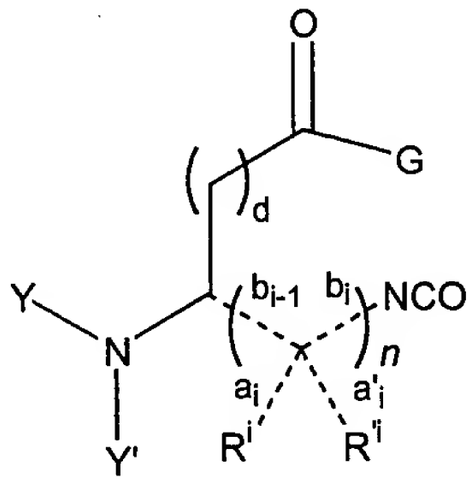
1/ cyclization between R^i and R'^i,

2/ cyclization between R^i (or R'^i) and R^{i+kc} (in which kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

and more particularly the compounds corresponding to formula (V) in which $1 \leq n \leq 4$, X = N-hydroxysuccinimide, A is an urethane or acyl group, and particularly the compounds in which p, q, m, h, v and t are comprised from 1 to 10 and preferably equal to 1 or 2, and preferably those in which A = Boc and Fmoc.

13. Compounds of formula (Vbis):



(Vbis)

in which

- "n" is a whole number greater than or equal to 1, comprised particularly by 1 to 4, and preferably 1 to 2,

– "d" is a whole number comprised from 0 to 4, preferably equaling 0 or 1,

– "i" is a whole parameter greater than or equal to 2 defined in the following manner: i takes all the whole values comprised from 2 to n+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = Ø; a'_1 and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_1 and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

certain of these bonds can also form parts of aromatic rings,

– the R_1, R_i, R'_i groups can each represent independently of each other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR_a$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the Y and Y' groups can be or contain:

1/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$A\text{-}N(Z_1)\text{-}C(Z'_1)(Z''_1)\text{-}\Psi_1[*]\text{-}\ldots\text{-}\Psi_{k-1}[*]\text{-}C(Z'_k)(Z''_k)\text{-}\Psi_k[*]\text{-}\ldots\Psi_{p-1}[*]C(Z'_p)(Z''_p)\text{-}\Psi_p[*]\text{-}$

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to p,

– A is a group selected from:

* hydrogen

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH{=}CH_2$),

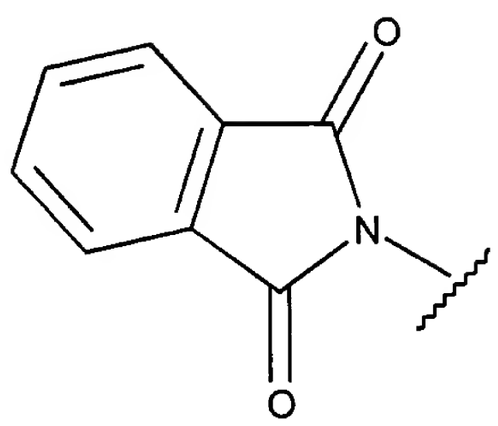
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,

* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,

* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R^1=Ø)



* biotin

– or Z_k, Z'_k, and Z''_k can each represent and independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-OR_b

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

$-CH_2CONH_2$

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– $-\psi_k[*]-$ are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

$\psi_k[*]- = -$ $-CH_2CH_2$; $-CH(F_k)=CH(F_k')-$; $-CH_2NH-$; $-NHCO-$; $-NHCONH-$; $-COCH_2-$; $-CH(OH)CH_2-$; $-CH(OH)CH_2NH-$; $-CH_2-$; $-CH(F_k)-$; $-CH_2O-$; $-CH_2-NHCONH-$; $CH(F_k)NHCONF_k'-$; $-CH_2-CONH-$; $CH(F_k)CONH-$; $-CH(F_k)CH(F_k')CONH-$

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

2/ an amino acid residue or an amino acid chain:

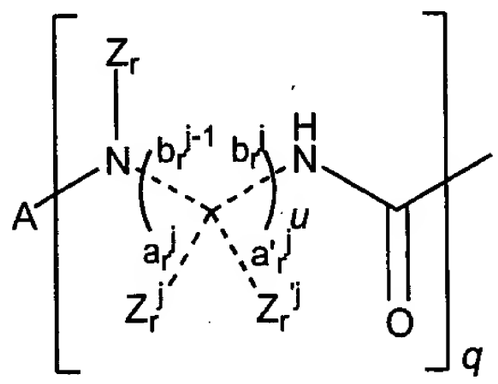
$A-N(Z_1)-C(Z'_1)(Z''_1)-CO-N(Z_2)-\ldots-CO-N(Z_k)-C(Z'_k)(Z''_k)-CO-N(Z_{k+1})-\ldots CO-N(Z_m)-C(Z'_m)(Z''_m)-CO-$

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to m,

– A defined as above

3/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the integer values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_q^1 and b_q^{n+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– A is as defined above,

– Z_r, Z_r^j, $Z'_r{}^j$ are defined as previously for R^1, R^i, R'^i, and R

– the group G can be or contain

A/ a pseudopeptide (peptide containing one or several pesudopeptide linkages)

$$-N(S_1)C(S'_1)(S''_1)-\Psi_1[*]-\ldots-\Psi_{k-1}[*]-C(S'_k)(S''_k)-\Psi_k[*]-\ldots\Psi_{h-1}[*]C(S'_h)(S''_h)-D$$

– "k" is a whole number varying from 1 to h,

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– D can be:

hydrogen,

-COOH

$-COOR_c$

$-CONH_2$

$-CH_2COOR_c$

-NHCOR

$-CONR_cR_d$

$-N(R_c)CON(R_d)$

-OH

$-OR_c$

-CN

$-C(O)R_c$

R_c and R_d representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_k, S'_k and S''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ -COOH

4/ -OH

5/ $-NHR_e$

6/ $-NH_2$

7/ $-NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

a halogen

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

– -ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

ψ_k[*]- = - -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; -CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F_k')$CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

B/ an amino acid residue or a chain of amino acid residues:

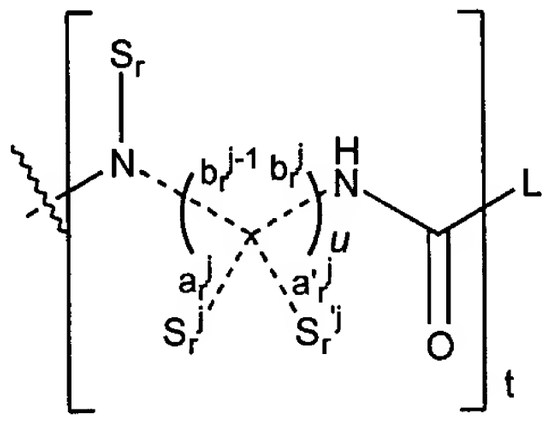
-$N(S_1)C(S'_1)(S''_1)$-CO-$N(S_2)$-…-CO-$N(S_k)$-$C(S'_k)(S''_k)$-CO-$N(S_{k+1})$-…CO-$N(S_v)$-$C(S'_v)(S''_v)$-D

– "v" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10 and preferably v>3 and v>5,

– "k" is a whole number varying from 1 to v,

– D, S_k, S'_k and S''_k are defined independently as above,

C/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the whole values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds a_r^j, $a'_r{}^j$, b_r^j and b_r^{j-1} can also form a part of aromatic rings,

– the group L can be:

$-NH_2$

$-NHR_f$

$-NR_fR_g$

R_f and R_g representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_r, S_r^j, $S'_r{}^j$ can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and, in the case of the proline, the groups S_r and $S'_r{}^j$ or S_r and S_r^j are linked together in order to give the proline cycle,

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_e$

2/ $-CONHR_e$

3/ -COOH

4/ -OH

5/ -OR_e

6/ NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group whose structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

-$COOR_e$

-$CONHR_e$

-$CONH_2$

-CH_2COOR_e

-CH_2CONHR_e

-CH_2CONH_2

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

the compounds of formula (Vbis) having the following property:

– if one or several asymmetric carbon atoms are present in formula (V), then their configuration can be independently of each other either R (rectus) or S (sinister),

– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations as follows:

1/ cyclization between R^i and R'^i

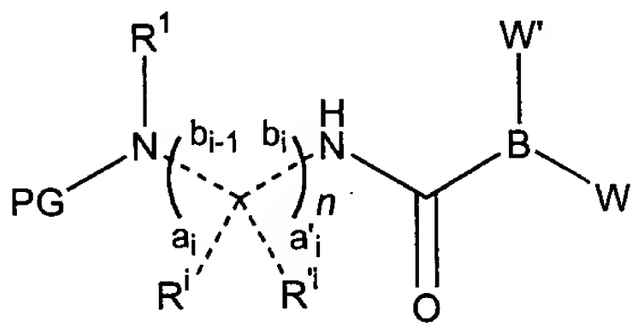
2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

and more particularly the compounds of the formula (Vbis) in which $1 \leq n \leq 4$, X = N-hydroxysuccinimide, A is an urethane or acyl group, and particularly the

compounds in which p, q, m, h, v and t are comprised from 1 to 10, and preferably equal to 1 or 2, and preferably those in which A = Boc and Fmoc.

14. Compounds of formula (VI)



(VI)

in which

– "n" is a whole number greater than or equal to 1, comprised particularly from 1 to 50, and preferably from1 to 10,

– "i" is a whole number varying from 2 to m+1,

– "a_i and a'_i", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_i and b_{i-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t), provided that:

* b_1 and b_{n+1} are always single bonds (s),
* if b_i = d, then a_i and a_{i+1} = s; a'_i and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if b_i = t, then a_i and a_{i+1} = Ø; a'_1 and a'_{i+1} = Ø; b_{i-1} and b_{i+1} = s
* if a_i = d, then b_{i-1} and b_i = s,

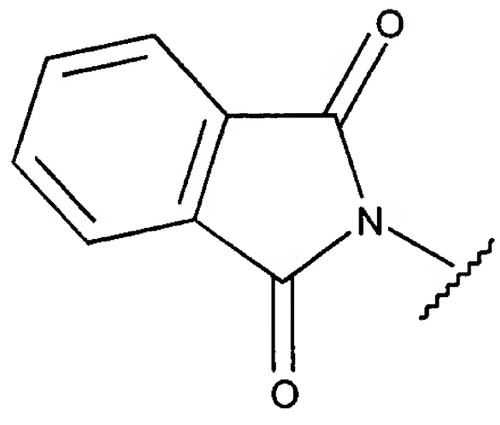
certain of these bonds can also form parts of aromatic rings,

– GP is a protective group selected from:

* urethane (GP = ROCO), preferably Boc (R = $C(CH_3)_3$), Fmoc (fluorenylmethoxycarbonyl), benzyloxycarbonyl (R = CH_2Ph), allyloxycarbonyl (R = $-CH_2CH=CH_2$),
* acyl (GP = RCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl, aryl,
* alkyl (GP = R), preferably R = trityl, CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, benzyl, allyl,
* aryl, particularly phenyl,

* urea (GP = RNHCO), preferably R = CH_3, CH_2CH_3, $CH(CH_3)_2$, $C(CH_3)_3$, phenyl, benzyl, allyl,

* phthalimide (R^1=Ø)



* O_2 (corresponds to a nitro group as a masked form of the amine), R^1 = Ø

– the R_1, R_i, R'_i and R groups can each represent independently of each other:

hydrogen,

halogen,

the side chain of an amino acid selected from natural or synthetic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_a$

2/ -$CONHR_a$

3/ -COOH

4/ -OH

5/ -OR_a

6/ -NHR_a

7/ -NH_2

8/ -$NH(CO)R_a$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl

12/ nitrile

13/ guanidine

14/ nitro

an aryl group whose cyclic structure contains 5 to 20 carbon atoms

an OR_a group

a NH_2 group

an OH group

$-COOR_a$

$-CONHR_a$

$-CONH_2$

$-CH_2COOR_a$

$-CH_2CONHR$

$-CH_2CONH_2$

R_a representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– the B group can be N or O,

– the W and W' groups can be or contain:

A/ hydrogen

B/ a (C1-C20) alkyl group unsubstituted or substituted with one or several substituents from the following:

1/ $-COOR_h$

2/ $-CONHR_h$

3/ -COOH

4/ -OH

5/ $-OR_h$

6/ -NHR

7/ $-NH_2$

8/ $-NH(CO)R_h$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_h representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

C/ an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

D/ a side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids, and in the case of proline, W = W' = $-CH_2-CH_2-CH_2-$ CH(COOR)-)

E/ a pseudopeptide (peptide containing one or several pseudopeptide linkages)

$-C(S'_1)(S''_1)-\Psi_1[*]-\ldots-\Psi_{k-1}[*]\,(S_k)-C(S'_k)(S''_k)-\Psi_k[*]-\ldots\Psi_{h-1}[*]C(S'_h)(S''_h)-D$

– "h" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– "k" is a whole number varying from 1 to h,

– D can be:

hydrogen,

-COOH

$-COOR_c$

$-CONH_2$

$-CH_2COOR_c$

$-NHCOR_c$

$-CONR'_cR'_d$

$-N(R_c)CON(R_d)$

-OH

$-OR_c$

-CN

$-C(O)R_c$

R_c and R_d representing independently of each other an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– S_k, S'_k and S''_k can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic and non-proteinogenic amino acids,

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -NHR_e

6/ -NH_2

7/ -$NH(CO)R_e$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

a halogen

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms.

– -ψ_k[*]- are independently either CO-NH peptide linkages or linkages of different chemical natures selected particularly from the following list:

ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$- ; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; -CH_2-CONH- ; $CH(F_k)CONH$- ; -$CH(F_k)CH(F_k')CONH$-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

F/ an amino acid residue or an amino acid chain:

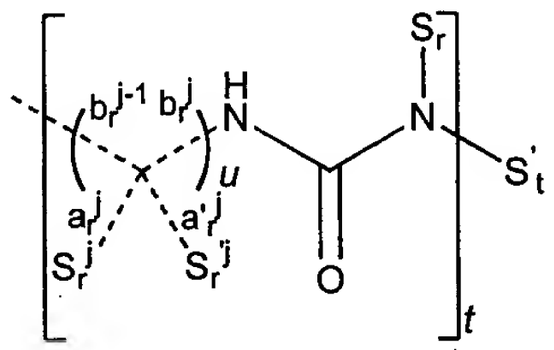
$-C(S'_1)(S''_1)-CO-N(S_2)-\ldots-CO-N(S_k)-C(S'_k)(S''_k)-CO-N(S_{k+1})-\ldots CO-N(S_v)-C(S'_v)(S''_v)-D$

– "v" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10, with preferably v>3 and v>5,

– "k" is a whole number varying from 1 to v,

– D, S_k, S'_k, and S''_k are independently defined as indicated above,

G/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "t" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter greater than or equal to 2 defined as follows: j takes all the integer values comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to t,

– "a_r^j and a'^j_r", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* b_t^1 and b_t^{u+1} are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; a'^j_r and a'^{j+1}_r = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; a'^j_r and a'^{j+1}_r = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

certain of these bonds can also form a part of aromatic rings,

– S_r, S_r^j, $S'_r{}^j$, S'_v can each represent independently:

hydrogen,

the side chain of an amino acid selected from natural and synthetic amino acids, and in the case of proline ($S_r^j = S'_r{}^j$ = -CH_2-CH_2-CH_2-CH(COOR)-)

a (C1-C20) alkyl group unsubstituted or substituted with one or several of the following substituents:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -OR_e

6/ -NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

an OR_e group

a NH_2 group

an OH group

-$COOR_e$

-$CONHR_e$

-$CONH_2$

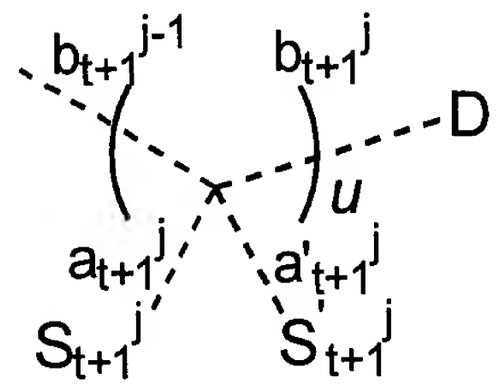
-CH_2COOR_e

-CH_2CONHR_e

-CH_2CONH_2

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

S'_t can also represent the group defined by the following formula:



S_{t+1}^{j}, S'_{t+1}^{j} having the meanings as indicated for S_r, S_r^j, $S'_r{}^j$ and S'_v,

D, u have the same meanings as indicated above,

– "a_{t+1}^{j} and $a'_{t+1}{}^{j}$", represented by a broken line, are covalent bonds which can be single (s) or double (d),

"$b_{t+1}{}^{j-1}$ and $b_{t+1}{}^{j}$", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

* $b_{t+1}{}^{j}$ and $b_{t+1}{}^{u+1}$ are always single bonds (s),
* if $b_{t+1}{}^{j} = d$, then $a_{t+1}{}^{j}$ and $a_{t+1}{}^{j+1} = s$; $a'_{t+1}{}^{j}$ and $a'_{t+1}{}^{j+1} = \emptyset$; $b_{t+1}{}^{j-1}$ and $b_r{}^{j+1} = s$
* if $b_{t+1}{}^{j} = t$, then $a_{t+1}{}^{j}$ and $a_{t+1}{}^{j+1} = \emptyset$; $a'_{t+1}{}^{j}$ and $a'_{t+1}{}^{j+1} = \emptyset$; $b_{t+1}{}^{j-1}$ and $b_r{}^{j-1} = s$
* if $a_{t+1}{}^{j} = d$, then $b_{t+1}{}^{j-1}$ and $b_{t+1}{}^{j} = s$,

the compounds of formula (VI) having the following property:

– if one or several asymmetric carbon atoms are present in formula (VI), then their configuration can be independently of each other either R (rectus) or S (sinister),

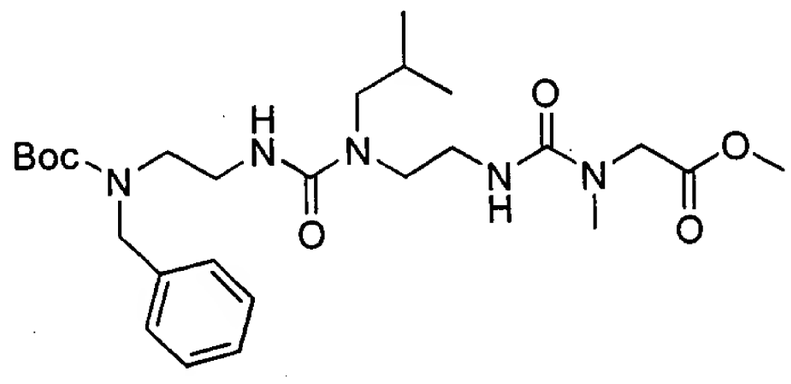
– the groups R^1, R^i, R'^i can also be defined on the basis of intramolecular cyclizations as follows:

1/ cyclization between R^i and R'^i

2/ cyclization between R^i (or R'^i) and R^{i+kc} (wherein kc is a positive whole number, preferably comprised from 1 to 3)

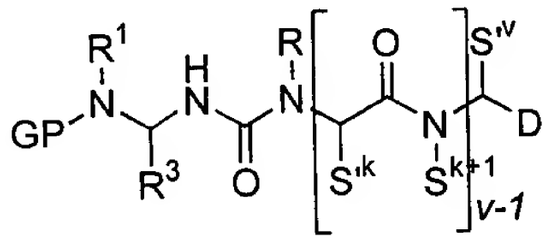
3/ cyclization between R^1 and R^i (or R'^i) wherein preferably i = 1, 2, 3 or 4,

provided that the compound of formula (VI) is different from:

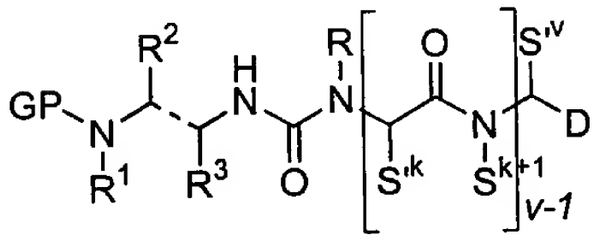


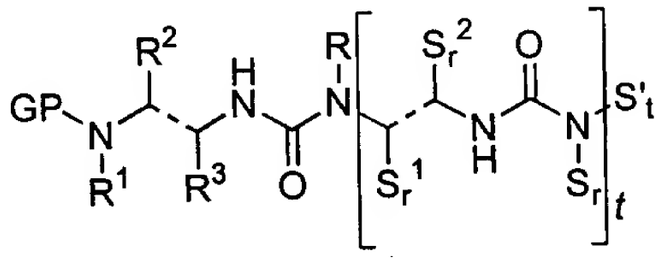
15. Compounds of formula (VI) in which $1 \leq n \leq 4$, and GP is an urethane or acyl group defined according to claim 12, and more particularly the following compounds for which v, and t are comprised from 1 to 10, and preferably equal to 1 or 2, and particularly those for which GP = Boc and Fmoc and O_2:

n=1

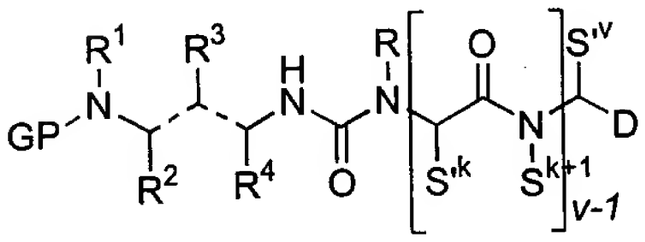


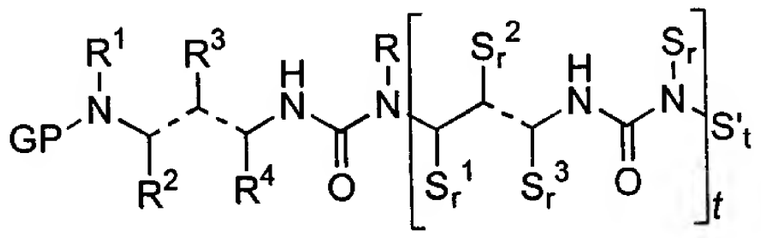
n=2



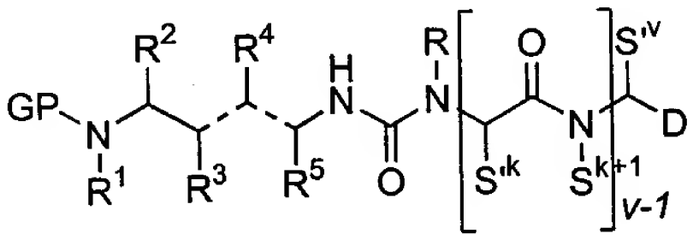


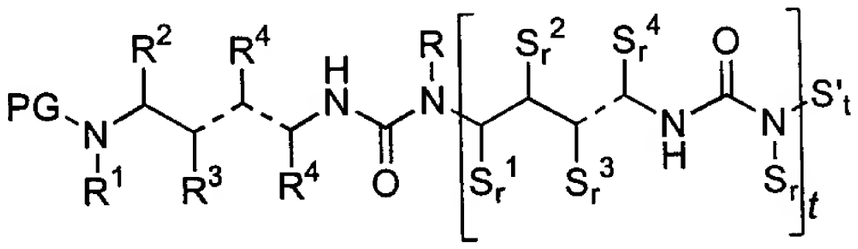
n=3

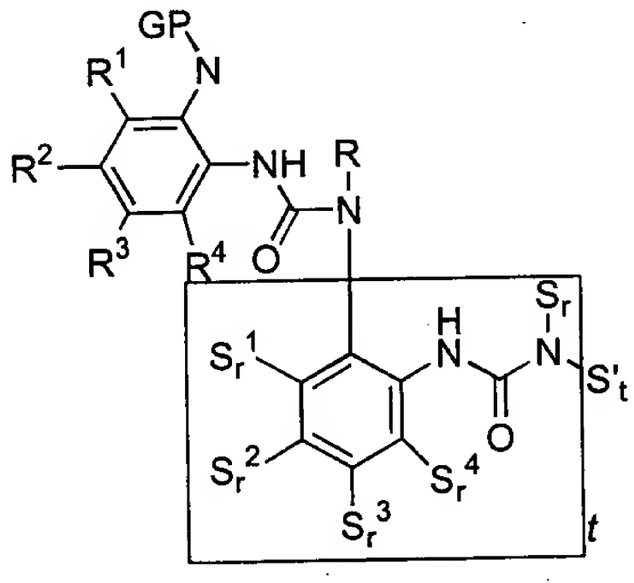


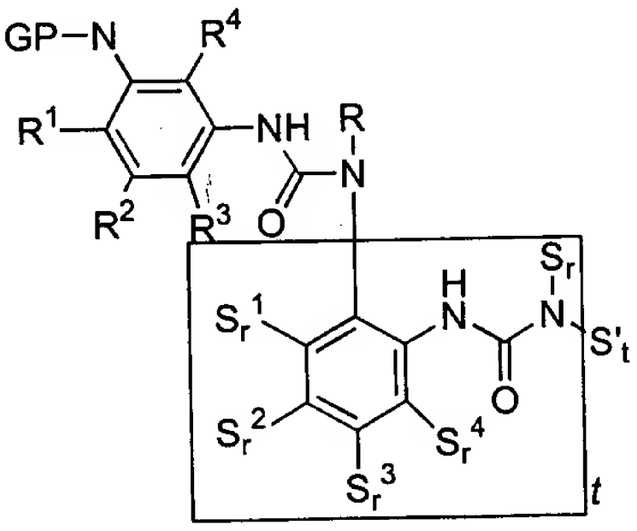


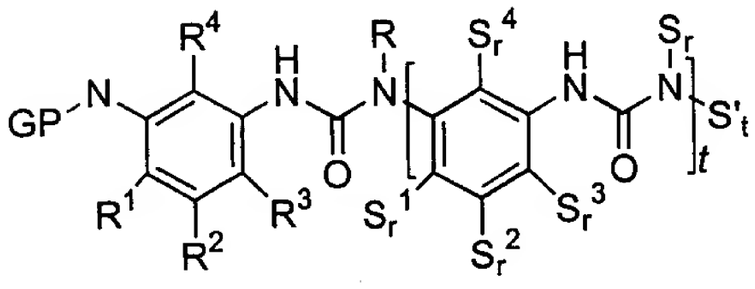
n=4

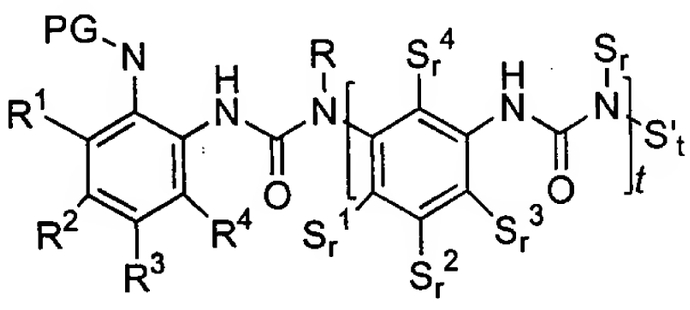






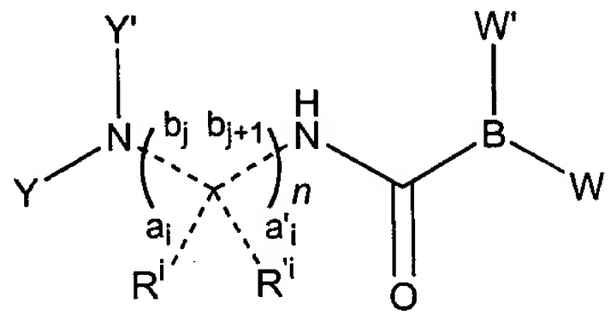






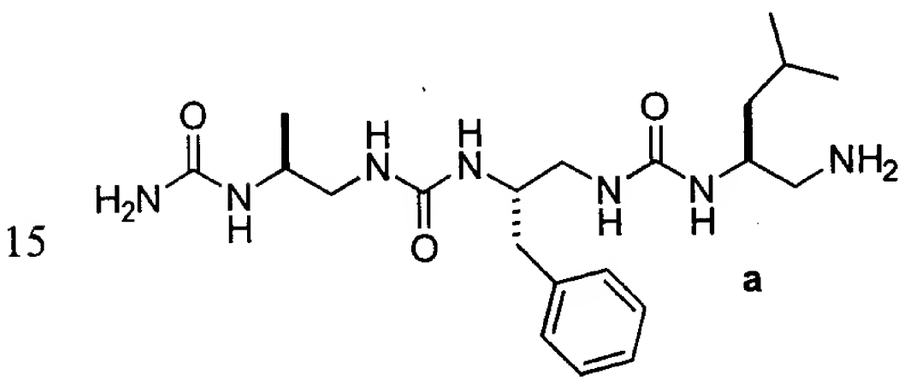
the broken lines corresponding to single or double bonds, with proviso that two double binds are not contiguous.

16. Compounds of formula (VII):

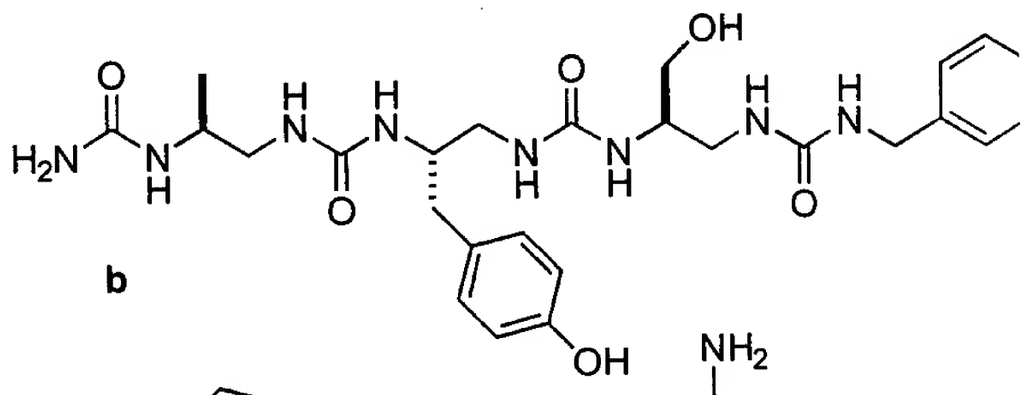


(VII)

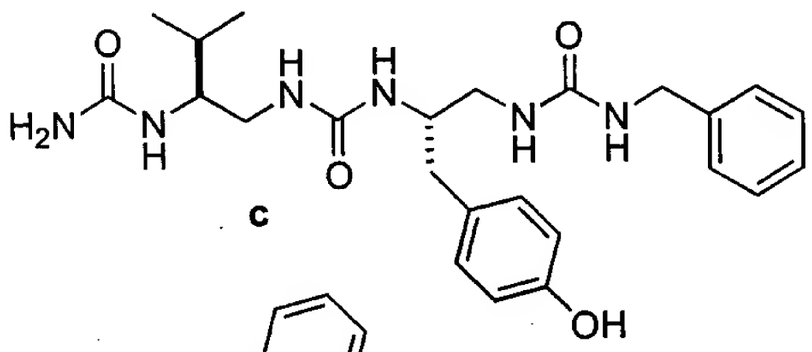
in which Y, Y', R_i, R'_i, B, W, W', a_i, a'_i, b_j, b_{j+1} have the meanings as indicated in claims 11, 14 and 15, provided that the compounds of following formulas are excluded:



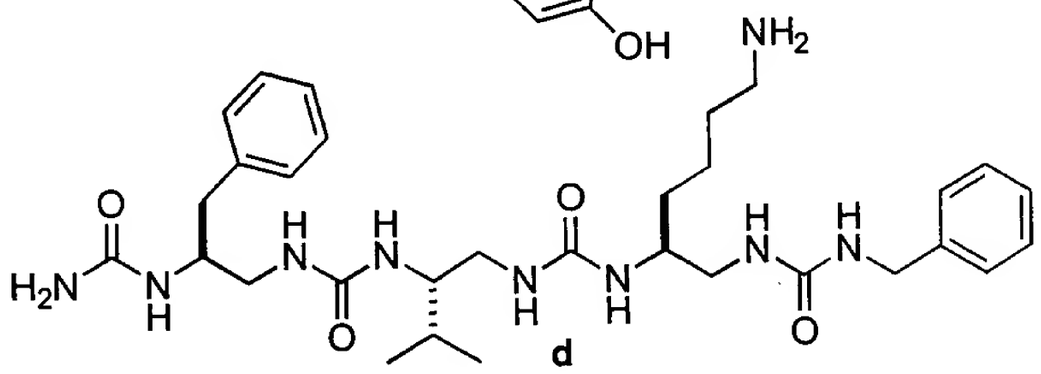
a



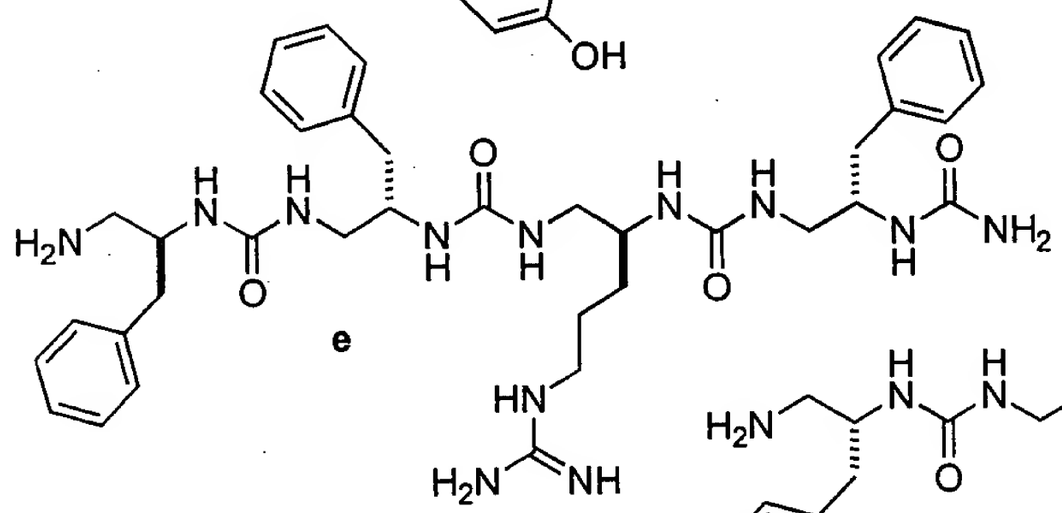
b



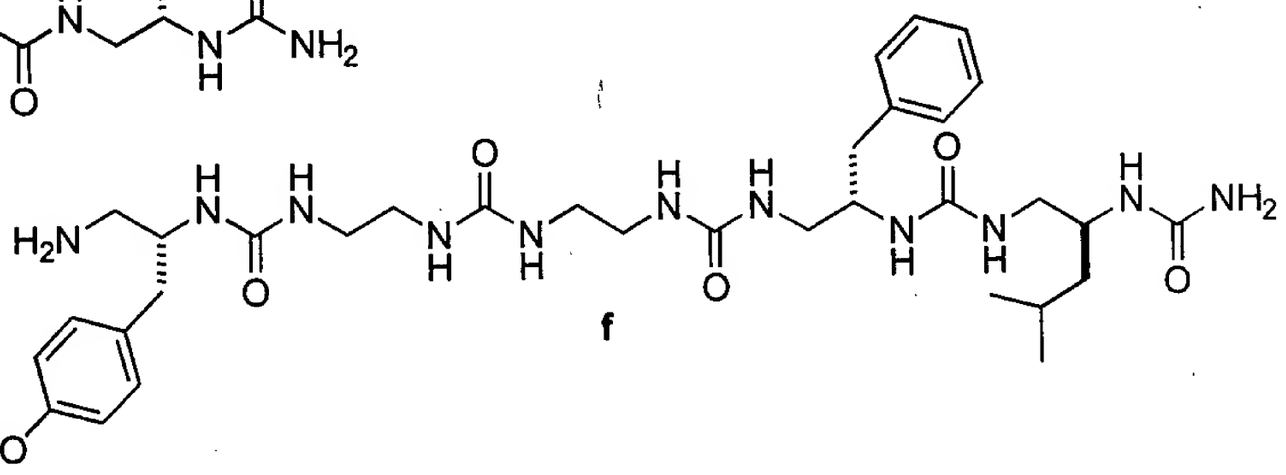
c



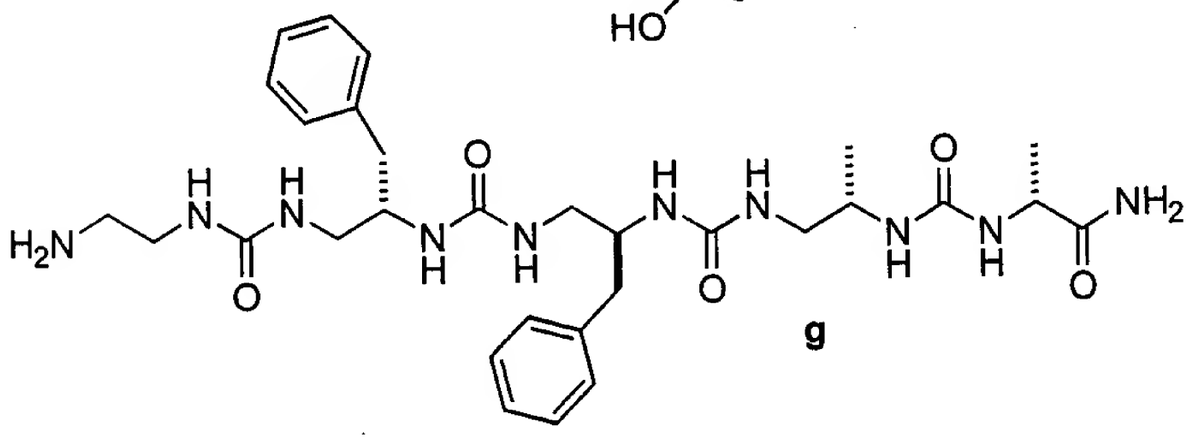
d



e

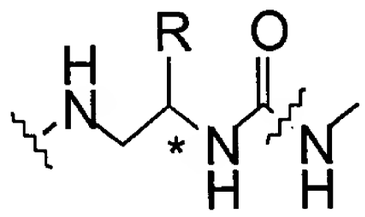


f



g

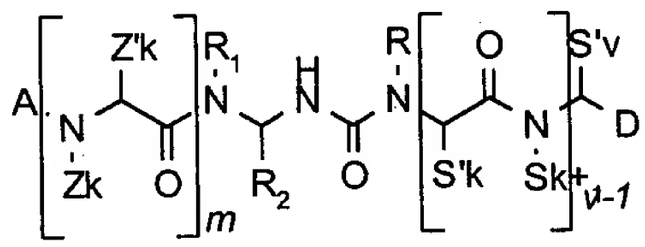
and provided that the compound of formula (VII) is different from the analogs of the peptide Tyr-Gly-Gly-Phe-Leu-OH, containing one or several derivatives as defined below mimicking the side chain of the amino acids present in the peptide and permitting the introduction of one or several urea linkages, which is to say the compound of formula (VII) is different from the following compounds:



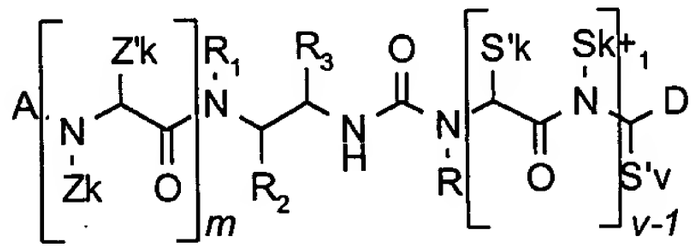
in which R represents hydroxybenzyl, a hydrogen atom, a benzyl group, or an isobutyl group.

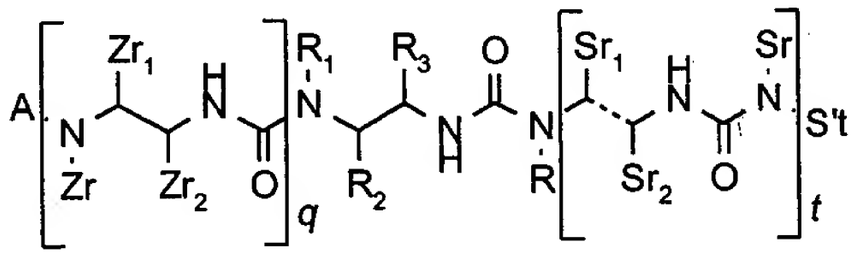
17. Compounds of formula (VII) in which $1 \leq n \leq 4$, , and particularly the following compounds for which v, t, m and q are comprised from 1 to 10, and preferably from 1 to 5, and more particularly the following compounds:

n=1

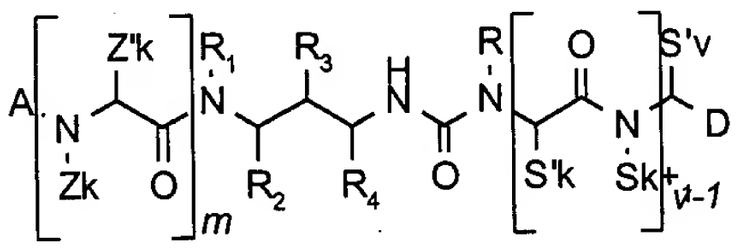


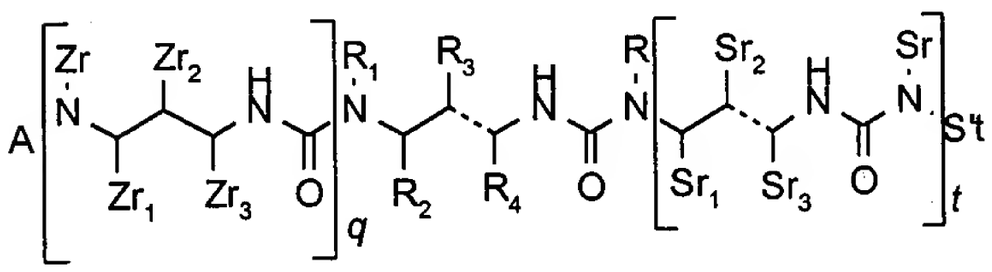
n=2



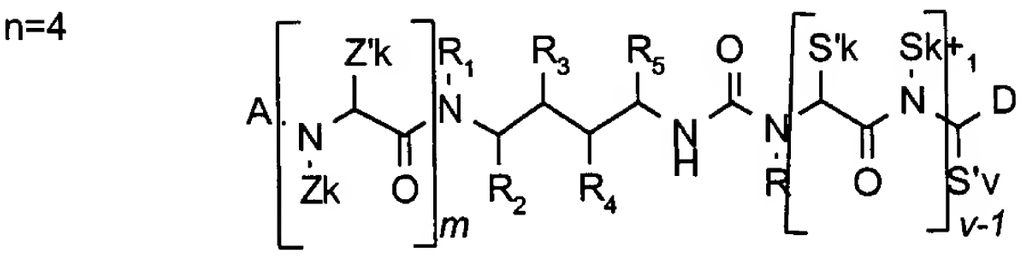


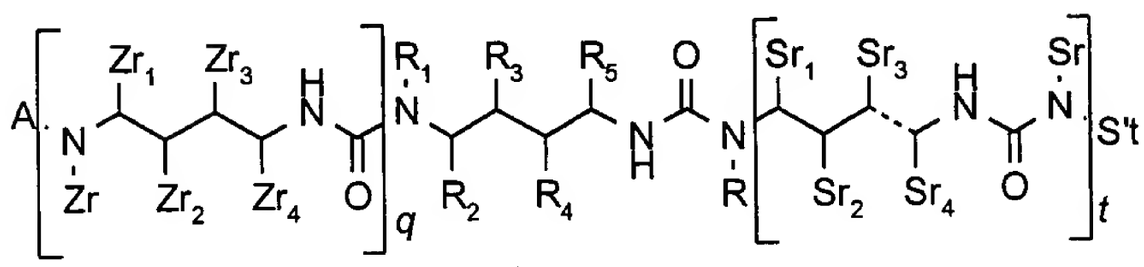
n=3



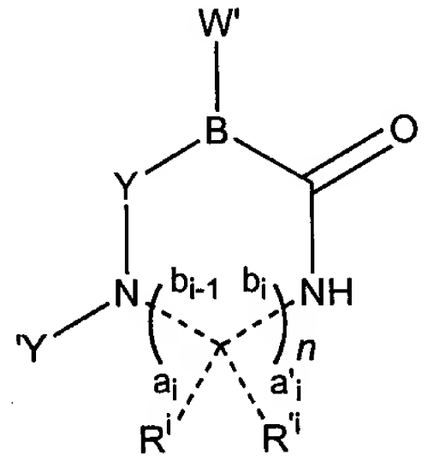


n=4





18. Compounds of formula (VIII)



(VIII)

in which:

the total number of atoms forming the cycle is greater than seven,

the groups R^i, R''^i, Y', W', B have the meanings already indicated above,

the group Y in this new case can be or contain:

I/ a (C1-C20) alkyl group, unsubstituted or substituted with one or more substituents from the following:

1/ -$COOR_e$

2/ -$CONHR_e$

3/ -COOH

4/ -OH

5/ -OR

6/ -NHR_e

7/ -NH_2

8/ -$NH(CO)R_e$

9/ aryl, whose cyclic structure contains 5 to 20 carbon atoms,

10/ halogen

11/ carbonyl of 1 to 10 carbon atoms

12/ nitrile

13/ guanidine

R_e representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

II/ an aryl group

III/ a pseudopeptide (peptide containing one or several pseudopeptidic linkages)

(on B←) -C(Z'$_1$)(Z''$_1$)-ψ_1[*]-...-ψ_{k-1}[*] (Z_k)-C(Z'$_k$)(Z''$_k$)-ψ_k[*]-...ψ_{p-1}[*]C(Z'$_p$)(Z''$_p$)-CO-(→ on NY')

– "p" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– Z_k, Z'$_k$ and Z"$_k$ can each represent independently of each other:

hydrogen,

the side chain of an amino acid selected from proteinogenic or non-proteinogenic amino acids

a (C1-C20) alkyl group, unsubstituted or substituted with one or several substituents from the following:

1/ -$COOR_b$

2/ -$CONHR_b$

3/ -COOH

4/ -OH, OR_b

5/ -NHR_b

6/ -NH_2

7/ -$NH(CO)R_b$

8/ aryl, whose cyclic structure contains 5 to 20 carbon atoms

9/ halogen

10/ carbonyl of 1 to 10 carbon atoms

11/ nitrile

12/ guanidine

an aryl group, whose cyclic structure contains 5 to 20 carbon atoms

a halogen

-$COOR_b$

-$CONHR_b$

-$CONH_2$

-CH_2COOR_b

-CH_2CONHR_b

-CH_2CONH_2

R_b representing an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

– -ψ_k[*]- are independently either CO-NH peptidic linkages or linkages of different chemical natures selected particularly from the following list:

-ψ_k[*]- = -CH_2CH_2 ; -$CH(F_k)$=$CH(F_k')$- ; -CH_2NH- ; -NHCO -; -NHCONH- ; -$COCH_2$- ; -$CH(OH)CH_2$- ; -$CH(OH)CH_2NH$- ; -CH_2- ; -$CH(F_k)$-; -CH_2O- ; -CH_2-NHCONH- ; $CH(F_k)NHCONF_k'$- ; CH_2-CONH- ; $CH(F_k)$CONH- ; -$CH(F_k)CH(F'_k)$CONH-

F_k and F_k' representing, independently of each other, hydrogen, halogen, an alkyl group of 1 to 20 carbon atoms, or an aryl group whose cyclic structure contains 5 to 20 carbon atoms,

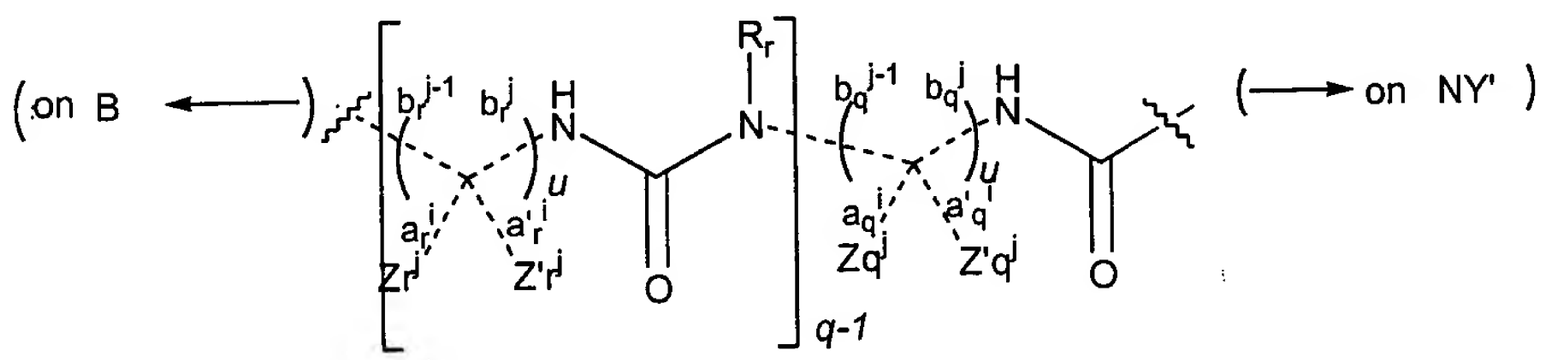
IV/ an amino acid residue or a chain of amino acid residues:

(on B←)-$C(Z'_1)(Z''_1)$-CO-$N(Z_2)$-…-CO-$N(Z_k)$-$C(Z'_k)(Z''_k)$-CO-$N(Z_{k+1})$-…CO-$N(Z_m)$-$C(Z'_m)(Z''_m)$-CO-(→ on NY')

– "m" is a whole number greater than or equal to 1, preferably from 1 to 50, preferably from 1 to 10,

– Z_k, Z'_k, and Z''_k are defined as before,

V/ an oligomer of urea defined as follows:



– "u" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "q" is a whole number greater than or equal to 1, preferably from 1 to 50, and preferably from 1 to 10,

– "j" is a whole parameter comprised from 2 to u+1,

– "r" is a whole parameter greater than or equal to 1 taking all the values comprised from 1 to q-1,

– "a_r^j and $a'_r{}^j$", represented by a broken line, are covalent bonds which can be single (s), or double (d),

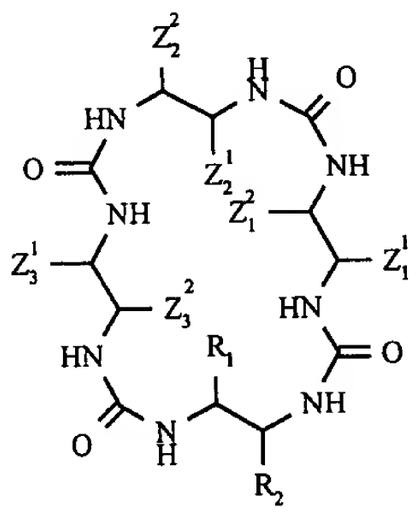
"b_r^j and b_r^{j-1}", represented by a broken line, are covalent bonds which can be single (s), double (d) or triple (t) provided that:

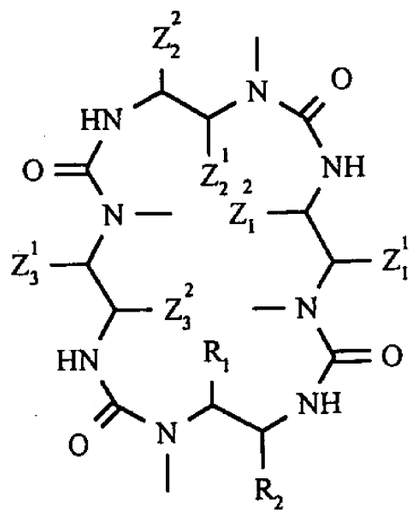
* $b_q{}^1$ and $b_q{}^{u+1}$ are always single bonds (s),
* if b_r^j = d, then a_r^j and a_r^{j+1} = s; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if b_r^j = t, then a_r^j and a_r^{j+1} = Ø; $a'_r{}^j$ and $a'_r{}^{j+1}$ = Ø; b_r^{j-1} and b_r^{j+1} = s
* if a_r^j = d, then b_r^{j-1} and b_r^j = s,

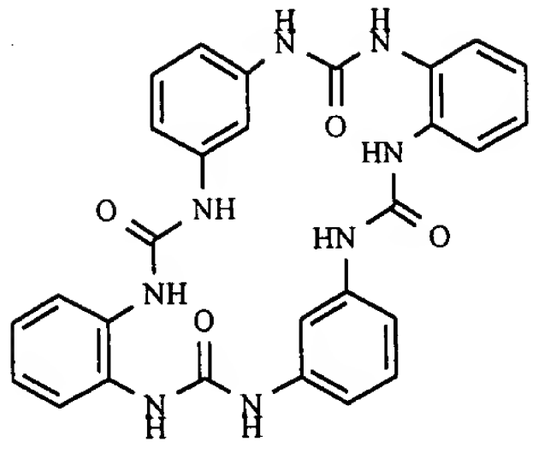
certain of these bonds can also form a part of aromatic rings,

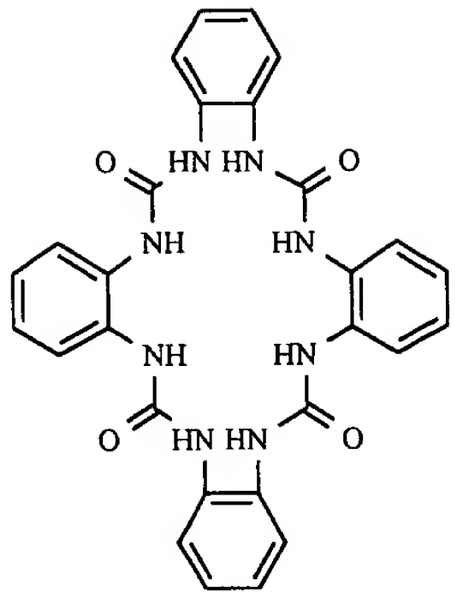
– Z_r, Z_r^j, $Z'_r{}^j$ have meanings indicated with respect to R^1, R^i, R^{ii} as defined above.

19. Compounds of formula (VIII) in which $1 \leq n \leq 4$, and particularly the following compounds in which h, v, t, p, m, and q are comprised from 1 to 10 and preferably from 1 to 5, and more particularly the following compounds:









in which R^1 and R^2 have the meanings indicated in claim 12 and in which Z_1^1, Z_1^2, Z_2^1, Z_2^2, Z_3^1 and Z_3^2 have the meanings indicated in claim 18.

20. Compounds of formula (III), (IV), (V), (Vbis), (VI) and (VII) according to any of claims 8 to 17, in which the aryl group is selected from:

1/ phenyl

2/ naphtyl

3/ indenyl

4/ thiophenyl

5/ benzothiophenyl

6/ furanyl

7/ benzofuranyl

8/ pyridyl

9/ indolyl

10/ pyrollyl

or the aryl group non substituted or substituted with 1 to 6 substituents selected particularly from:

1/ alkyl of 1 to 10 carbon atoms

2/ halogen

3/ alkoxy of 1 to 10 carbon atoms

4/ hydroxyl

5/ amine of 1 to 10 carbon atoms

6/ ester of 1 to 10 carbon atoms

7/ nitrile

8/ aryl, whose cycle structure contains 5 to 20 carbon atoms

9/ nitro

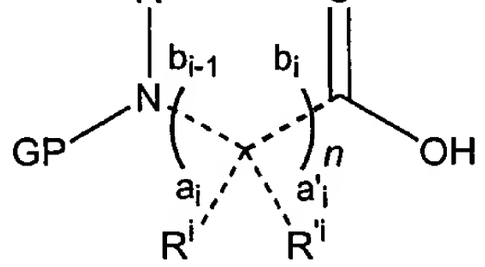
10/ urea of 1 to 10 carbon atoms

11/ amide of 1 to 10 carbon atoms

12/ guanidine.

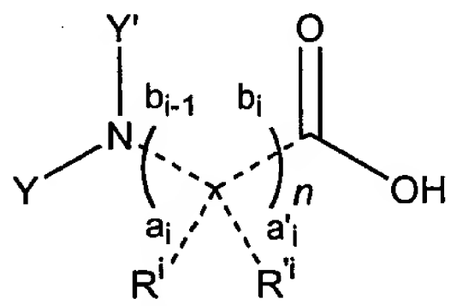
21. Process for the preparation of the derivatives of formula (I), (II), (III), (IV), (V) or (V bis) according to any of claims 3 to 13, from respectively:

– compounds of formula (IX) (for compounds of formula (I) and (II))



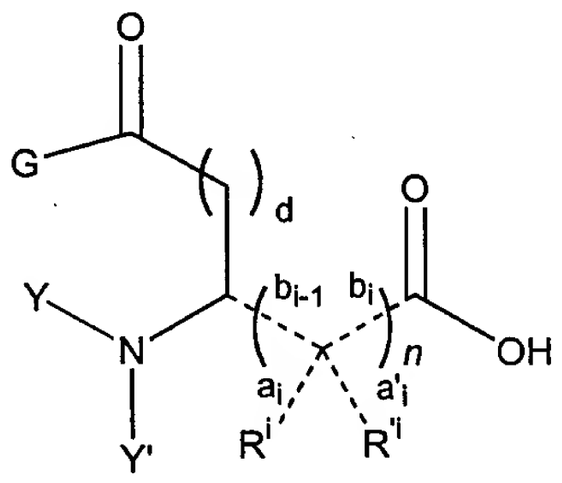
(IX)

– compounds of formula (X) (for compounds of formula (III) and (IV))



(X)

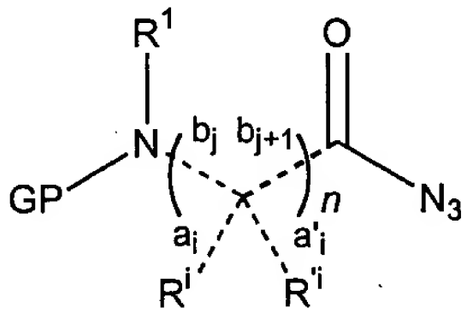
– compounds of formula (XI) (for compounds of formula (V) and (V bis))



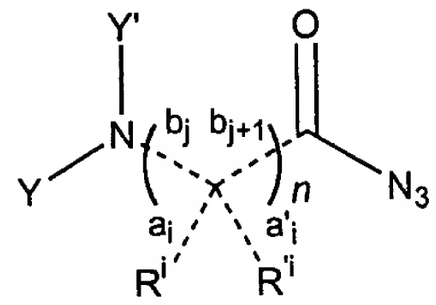
(XI)

comprising

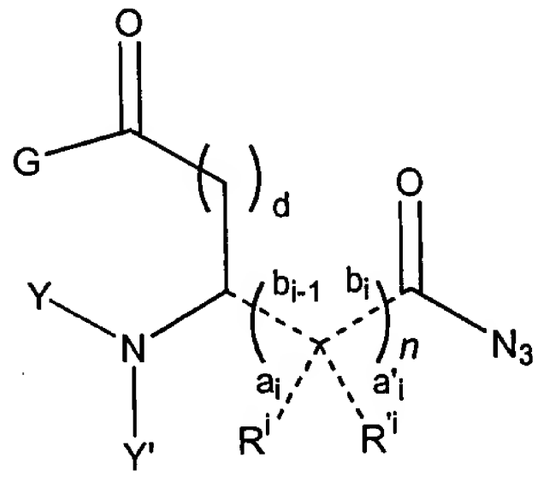
(a) a step of transformation of the acid (IX) or (X) or (XI) into a corresponding acyl azide (XII) or (XIII) or (XIV) respectively,



(XII)



(XIII)



(XIV)

for example by treatment of the mixed anhydride (formed by reaction of acid (IX), (X) or (XI) with ethyl or isobutyl chloroformate in the presence of a tertiary amine such as NMM (N-methylmorpholine), DIEA (di-isopropylethylamine) or Et_3N in THF (tetrahydrofurane at -15°C)) with a sodium azide solution,

(b) a step of transformation of the acyl azide (XII) or (XIII) or (XIV) by Curtius rearrangement into the corresponding isocyanate (II) or (IV) or (Vbis), respectively,

for example by heating a solution of the acyl azide in a suitable solvent, particularly toluene or xylene (for example at 65°C), the formation of the isocyanate being followed by observation of the release of gas into the balloon, the end of the gaseous emission signifying completion of the Curtius rearrangement,

(c) a step of treatment of the isocyanate (II), (IV) or (V bis), preferably not isolated, the isocyanate being in solution, for example in hot toluene (65°C for example), with one of the derivatives from the following list:

- N-hydroxysuccinimide
- phenol
- pentafluorophenol
- pentachlorophenol
- p-nitrophenol
- 2,4-dinitrophenol
- 2,4,5-trichlorophenol

- 2,4-dichloro-6-nitrophenol
- hydroxy-1,2,3-benzotriazole
- imidazole
- tetrazole
- 1-oxo-2-hydroxydihydrobenzotriazine (HODhbt)
- 7-aza-1-hydroxybenzotriazole (HOAt)
- 4-aza-1-hydroxybenzotriazole (4-HOAt)

(permitting obtaining a pre-activated synthon) and if desired a base such as pyridine, to obtain a carbamate of formula (I), (III) or (V), which is then advantageously isolated, preferably by crystallization or by purification, particularly on a silica column, or by HPLC or by aqueous, acid or basic washing after dissolution in an organic solvent.

22. Process for the preparation of compounds of formula (VI), (VII) or (VIII) according to any of claims 14 to 18, comprising the reaction of compounds containing primary or secondary amines, with one of the products of formula (I), (II), (III), (IV), (V) or (Vbis) according to any of claims 1 to 13, for example in a solvent such as DMF, H_2O/acetone, THF or dichloromethane with or without the addition of a base such as Et_3N, DIEA, NMM, Na_2CO_3.